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[Intervention Review]

Interventions for itch in people with advanced chronic kidney disease

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ABSTRACT

Background

Itch in patients with chronic kidney disease (CKD) is common, often very distressing and associated with depression, reduced quality of life, and increased death. The most common first-line treatment has been the use of antihistamines despite the lack of substantial evidence for its use for uraemic itch. Few recommendations and guidelines exist for treatment.

Objectives

We aimed to determine: 1) the benefits and harms (both absolute and relative) of all topical and systemic interventions for the treatment of uraemic itch, either alone or in combination, when compared with placebo or standard care; and, 2) the dose strength or frequency, stage of kidney disease or method of dialysis used (where applicable) in cases where the effects of these interventions vary depending on co-interventions.

Search methods

We searched the Cochrane Kidney and Transplant Register of Studies up to 17 December 2019 through contact with the Information Specialist using search terms relevant to this review. Studies in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE, conference proceedings, the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Selection criteria

Randomised controlled trials (RCTs) in adults with CKD stages 4 or 5 comparing treatments (pharmacological, topical, exposure, dialysis modality) for CKD associated itch to either placebo or other established treatments.

Data collection and analysis

Two authors independently abstracted study data and assessed study quality. Data were analysed using a random effects meta-analysis design estimating the relative effects of treatment versus placebo. Estimates of the relative effects between treatments are included where possible. For continuous measures of severity of itch up to three months, mean difference (MD) or standardised mean difference (SMD) were used. When reported, adverse effects were tabulated. The certainty of the evidence was estimated using GRADE.

Main results

Ninety-two RCTs, randomising 4466 participants were included. Fifty-eight studies (3285 participants) provided sufficient data to be meta-analysed. Of these, 30 compared an intervention to a placebo or control. The 10 cm Visual Analogue Scale (VAS) was the dominant instrument utilized for itch reporting and the Duo score was used in a minority of studies.

GABA analogues including, gabapentin and pregabalin, reduce itch in patients with CKD (5 studies, 297 participants: 4.95 cm reduction, 95% CI 5.46 to 4.44 lower in VAS compared to placebo; high certainty evidence). Kappa opioid agonists, including nalfurafine also reduced itch in this population (6 studies, 661 participants: 1.05 cm reduction, 95% CI 1.40 to 0.71 lower in VAS compared to placebo; high certainty evidence). Ondansetron had little or no effect on itch scores (3 studies, 183 participants: 0.38 cm reduction, 95% CI 1.04 lower to 0.29 higher in VAS compared to placebo; high certainty evidence). Reduction in the severity of itch was reported with oral montelukast, turmeric, zinc sulfate and topical capsaicin. For all other interventions, the certainty of the evidence was low to moderate, and the interventions had uncertain effects on uraemic pruritus.

Six studies have disclosed significant financial support from their respective manufacturers, six were affected by lack of blinding, and 11 studies have 15 participants or less. Older, smaller RCTs often failed to follow intention-to-treat protocols with unexplained dropouts after randomisation.

Adverse effects were generally poorly and inconsistently reported across all RCTs. No severe adverse events were reported for any intervention.

Authors' conclusions

The RCTs of this meta-analysis contain a large array of interventions with a diverse set of comparators. For many interventions, trials are sparse. This served to make informative meta-analysis challenging.

Of all treatments for uraemic pruritus, gabapentinoids (gabapentin and pregabalin) were the most studied and show the greatest reduction in itch scores. Further RCTs, even of the scale of the largest trials included in this review, are unlikely to significantly change this finding. Kappa-opioid agonists (mainly nalfurafine) also may reduce itch, but indirect comparison suggests a much more modest effect in comparison to GABA analogues.

Evidence for oral montelukast, turmeric, zinc sulfate, and topical capsaicin also showed an itch score reduction. However, these reductions were reported in small studies, and warrant further investigation. Ondansetron did not reduce itch. It is somewhat unlikely that a further study of ondansetron will change this result.

PLAIN LANGUAGE SUMMARY

What is the best treatment for itch in people with chronic kidney disease?

What is the issue? Itch (medical term pruritus) is a common problem for people with chronic kidney disease (CKD). Itch can greatly affect quality of life and may lead to depression or increased risk of death. There are no widely used or agreed upon treatment guidelines for itch associated with CKD.

What did we do? We found 92 studies involving 4466 people investigating 30 treatments for CKD-associated itch. The control treatment was either placebo or (less commonly) another treatment for CKD-associated itch.

What did we find? One type of drug (gabapentin and pregabalin), an analogue to a common neurotransmitter appear to reduce itch in patients with CKD. Ondansetron, an anti-nausea drug, was another well studied treatment and appears have no significant association with itch reduction. Kappa-opioid drugs (nalfurafine) appear to slightly reduce itch. There is too little information on the remaining treatments for any thorough assessment of their efficacy in relieving itch or whether there is any anti-itch effect at all.

The three drugs mentioned above are well studied with higher quality evidence. The other treatments studied are of lower to moderate quality.

The studies seldom document a comprehensive list of adverse or side effects incurred during treatment. However, none of the adverse effects documented were severe. Further meaningful assessment on harm cannot be made.

Conclusions Drugs that work like neurotransmitters (gabapentin and pregabalin) reduce itch in patients with CKD. Other intervention either do not work, do not work as well, or need further study to make a conclusion.

SUMMARY OF FINDINGS

Summary of findings 1. Pharmacological interventions versus placebo for the relief of itch in people with advanced chronic kidney disease

Pharmacological interventions versus placebo for the relief of itch in people with advanced chronic kidney disease

Patient or population: uraemic pruritus

Settings: outpatient and multi-centre

Intervention: pharmacological treatments

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative Effect (95% CI)	No. of participants (RCTs)	Quality of the evidence (GRADE)
	Reduction of risk of placebo	Reduction of risk with pharmacological interventions			
GABA analogue **VAS (0 to 10 cm)**	The mean VAS score of the placebo group ranged from **0.8 to 2 cm lower** than pretreatment scores	The **mean reduction** in VAS score of the GABA analogue group was **4.95 cm lower** (5.46 to 4.44 lower) than placebo	-	297 (5)	⊕⊕⊕⊕ HIGH
Ondansetron **VAS (0 to 10 cm)**	The mean VAS score of the placebo group ranged from **0.1 to 2 cm lower** than pretreatment scores	The **mean reduction** in VAS score of the ondansetron agonist group was **0.38 cm lower** (1.04 lower to 0.27 higher) than placebo	-	183 (3)	⊕⊕⊕⊕ HIGH
Kappa-opioid agonist **VAS (0 to 10 cm)**	The mean VAS score of the placebo group ranged from **1.3 to 1.9 cm lower** than pretreatment scores	The **mean reduction** in VAS score of the kappa-opioid agonist group was **1.05 cm lower** (1.40 to 0.70 lower) than placebo	-	661 (5)	⊕⊕⊕⊕ HIGH
Mu-opioid antagonist **VAS (0 to 10 cm)**	The mean VAS score of the placebo group ranged from **0.5 to 1 cm lower** than pretreatment scores	The **mean reduction** in VAS score of the mu-opioid antagonist group was **4.29 cm lower** (10.24 lower to 1.66 higher) than placebo	-	62 (2)	⊕⊕⊖⊖ LOW[1,2]
Nalbuphine **VAS (0 to 10 cm)**	The mean VAS score of the placebo group was **3.2 cm lower** than pretreatment scores	The **mean reduction** in VAS score of the nalbuphine group was **0.75 cm lower** (1.70 lower to 0.20 higher) than placebo	-	179 (1)	⊕⊕⊖⊖ LOW[2,3]

Cromolyn **VAS (0 to 10 cm)**	The mean VAS score of the placebo group was **3 cm lower** than pretreatment scores	The **mean reduction** in VAS score of the cromolyn group was **4.8 cm lower** (7.03 to 2.57 lower) than placebo	-	40 (1)	⊕⊕⊖⊖ LOW[1,2]
Nicotinamide **VAS (0 to 5 cm)**	The mean VAS score of the placebo group was **1.7 cm lower** than pretreatment scores	The **mean reduction** in VAS score of the nicotinamide group was **0.47 cm higher** (0.32 lower to 1.26 higher) than placebo	-	50 (1)	⊕⊕⊖⊖ LOW[1,2]
EPO **Duo score (0 to 40)**	The mean Duo score of the placebo group was **1.5 lower** than pretreatment scores	The **mean reduction** in Duo score of the EPO group was **14.5 lower** (38.78 lower to 9.78 higher) than placebo	-	20 (1)	⊕⊖⊖⊖ VERY LOW[1,2,3]
Cholestyramine **0 to 3 severity scale**	The mean itch score of the placebo group ranged from **1.3 to 0.7 lower** than pretreatment scores	The **mean reduction** in VAS score of the cholestyramine group was **0.24 higher** (0.38 lower to 0.86 higher) than placebo	-	15 (2)	⊕⊕⊖⊖ LOW[1,4]
Montelukast **Duo score (0 to 81) and VAS (0 to 10 cm)**	The mean Duo score and VAS of the placebo group was **7 points and 0.5 cm lower** (respectively) than pretreatment scores.	The**SMD reduction** of the montelukast group was **1.4 lower** (1.87 to 0.92 lower) than placebo	-	87 (2)	⊕⊕⊕⊖ MODERATE[5]
Sertraline **VAS (0 to 10 cm)**	The mean VAS score of the placebo group was **3.7 lower** than pretreatment scores	The **mean reduction** in VAS score of the sertraline group was **1.8 cm lower** (3.65 lower to 0.05 higher) than placebo	-	46 (1)	⊕⊕⊖⊖ LOW[1,2]
Lidocaine Itch relief	167 per 1000	**800 per 1000** (221 to 1000)	**4.80** (0.78 to 29.50)	16 (1)	⊕⊖⊖⊖ VERY LOW[1,2,3]
Sodium thalidomide Itch relief	133 per 1000	**556 per 1000** (177 to 1000)	**4.17** (1.08 to 16.15)	33 (1)	⊕⊖⊖⊖ VERY LOW[1,2,3]
Doxepin Itch relief	208 per 1000	**875 per 1000** (396 to 1000)	4.20 (1.90 to 9.30)	48 (1)	⊕⊕⊖⊖ LOW[1,2]

The reduction of risk of pharmacological versus placebo (column 3) is the additional risk reduction in addition to the benefit provided by the placebo. "Lower" indicates a reduction or negative numerical change versus baseline.

CI: Confidence interval; **SMD**: standardised mean difference; **RR:** Risk Ratio; **VAS**: visual analogues scale

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Evidence of certainty was downgraded one level because of the reliance of the estimated effect on a small number of participants
[2]Evidence of certainty was downgraded one level because of the imprecise treatment estimate
[3]Evidence of certainty was downgraded one level because of study risks of bias
[4]Evidence of certainty was downgraded one level because heterogeneous results utilizing nonvalidated itch scoring methods
[5]Evidence of certainty was downgraded one level as homogeneity was difficult to assess (due to well validated but different itch scoring methods) and that the analysis would benefit from a greater number of participants

Summary of findings 2. Topical treatments versus placebo for the relief of itch in people with advanced chronic kidney disease

Topical treatments versus placebo for the relief of itch in people with advanced chronic kidney disease

Patient or population: uraemic pruritus

Settings: outpatient and multi-centre

Intervention: topical treatments

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		No. of participants (RCTs)	Quality of the evidence (GRADE)
	Reduction of risk of placebo	Reduction of risk with topical treatments		
Capsaicin cream **VAS and Duo's score**	The mean VAS and Duo score of this vehicle group was **1.7 cm and 13.4 lower** (respectively) than pretreatment scores.	The SMD of the capsaicin group was **0.84 lower** (1.22 to 0.45 lower) than vehicle	112 (2)	⊕⊕⊕⊖ MODERATE[1]
Pramoxine lotion **VAS (0 to 10 cm)**	The mean VAS score of this vehicle group was **1.4 cm lower** than pretreatment scores.	The mean reduction in VAS score of the pramoxine lotion group was **1.97 lower** (6.06 lower to 2.12 higher) than vehicle	27 (1)	⊕⊖⊖⊖ VERY LOW[2,3,4]
Calcineurin inhibitor **VAS (0 to 10 cm)**	The mean VAS score of this vehicle group was **7.1 cm lower** than pretreatment scores.	The mean reduction in VAS score of the calcineurin inhibitor group was **1.2 higher** (0.36 lower to 2.76 higher) than vehicle	80 (2)	⊕⊖⊖⊖ VERY LOW[2,3,4]

Dead Sea lotion **1 to 5 severity score**	The mean severity score of this vehicle group was **3 lower** than pretreatment scores.	The mean reduction in severity score of the Dead Sea Lotion group was **2 lower** (4.31 lower to 0.31 higher) than vehicle	41 (1)	⊕⊝⊝⊝ VERY LOW[2,3,4]
Cromolyn cream **VAS (0 to 5 cm)**	The mean VAS score of this vehicle group was **1.4 cm lower** than pretreatment scores.	The mean reduction in VAS score of the cromolyn cream group was **0.8 cm lower** (1.98 lower to 0.38 higher) than vehicle	60 (1)	⊕⊕⊝⊝ LOW[2,3]
Baby oil **Itch Severity Scale (0 to 21)**	The mean Itch Severity Scale of this vehicle group was **1 lower** than pretreatment scores.	The mean reduction in Itch Severity Scale of the baby oil group was **2.36 lower** (3.29 to 1.44 lower) than vehicle	125 (2)	⊕⊕⊝⊝ LOW[5]
L-arginine salve **0 to 3 severity score**	The mean severity score of this vehicle group was **3.4 lower** than pretreatment scores.	The mean reduction in severity score of the L-arginine salve group was **0.58 lower** (1.86 lower to 0.7 higher) than vehicle	48 (1)	⊕⊕⊝⊝ LOW[2,3]
Polyunsaturated fatty acids **VAS (0 to 10 cm)** **Duo score**	The mean VAS and Duo score of this vehicle group was **1 cm lower and 5 points higher** (respectively) than pretreatment scores.	The SMD of the polyunsaturated fatty acids group was **0.91 lower** (1.99 lower to 0.17 higher) than vehicle	78 (2)	⊕⊕⊝⊝ LOW[2,6]

The reduction of risk of pharmacological versus placebo (column 3) is the additional risk reduction in addition to the benefit provided by the placebo. "Lower" indicates a reduction or negative numerical change versus baseline.

CI: Confidence interval; **SMD**: standardised mean difference; **VAS**: visual analogue scale

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Evidence of certainty was downgraded one level as homogeneity was difficult to assess (due to well validated but different itch scoring methods) and that the analysis would benefit from a greater number of participants
[2]Evidence of certainty was downgraded one level because of the reliance of the estimated effect on a small number of participants
[3]Evidence of certainty was downgraded one level because of the imprecise treatment estimate
[4]Evidence of certainty was downgraded one level because of study risks of bias
[5]Evidence of certainty was downgraded two levels because of study risks of bias and use of a non-validated itch scoring method.
[6]Evidence of certainty was downgraded one level because of the imprecise and small treatment estimate

Summary of findings 3. Supplements, haemodialysis modalities, and other treatments for the relief of itch in people with advanced chronic kidney disease

Supplements, HD modalities, and other treatments for the relief of itch in people with advanced chronic kidney disease

Patient or population: uraemic pruritus

Settings: outpatient and multi-centre

Intervention: supplements, HD modalities, and other treatments

Comparison: placebo; other HD comparators

Outcomes	Anticipated absolute effects* (95% CI)		No. of participants (RCTs)	Quality of the evidence (GRADE)
	Reduction of risk of comparator	Reduction of risk with supplements, HD modalities, and other treatments		
Polyunsaturated fatty acids **0 to 5 severity score**	The mean severity score of this placebo group was **1.6% lower** than pretreatment scores.	The mean reduction in 0 to 5 severity score of the polyunsaturated fatty acids group was **11.3% lower** (9.0 to 3.6 lower) than placebo	22 (1)	⊕⊕⊖⊖ LOW[1,2]
L-carnitine **VAS (0 to 6 cm)**	The mean VAS score of this placebo group was **0.2 higher** than pretreatment scores.	The mean reduction in VAS score of the L-carnitine group was **0.26 lower** (2.85 lower to 2.43 higher) than placebo	12 (1)	⊕⊕⊖⊖ LOW[1,2]
Zinc sulfate **VAS (0 to 10 cm)**	The mean VAS and Duo score of this vehicle group was **4.3 cm and 6.1 lower** (respectively) than pretreatment scores.	The mean reduction of the zinc sulfate group was **1.77 lower** (2.88 to 0.66 lower) than placebo	76 (2)	⊕⊕⊕⊖ MODERATE[1]
Ergocalciferol **21 point scale**	The mean score of this vehicle group was **6.1 lower** than pretreatment scores.	The mean reduction in VAS score of the ergocalciferol group was **0.4 higher** (2.52 lower to 3.32 higher) than placebo	50 (1)	⊕⊕⊖⊖ LOW[1,2]
Turmeric **Duo score (5 to 40)**	The mean Duo's score of this vehicle group was **2 lower** than pretreatment scores.	The mean reduction in VAS score of the turmeric group was **6.4 lower*** (7.42 to 5.38 lower) than placebo	100 (1)	⊕⊕⊕⊖ MODERATE[1]
Fumaria parviflora **VAS (0 to 10 cm)**	The mean VAS score of this vehicle group was 2.2**lower** than pretreatment scores.	The mean reduction in VAS score of the Fumaria parviflora group was 3.90**lower** (5.04 to 2.76 lower) than placebo	63 (1)	⊕⊕⊖⊖ LOW[1,3]

High flux/permeability dialysis **VAS (0 to 10 cm)**	The mean VAS score of this control group ranged from **0.6 cm to 5.6 cm lower** than pretreatment scores.	The mean reduction in VAS score of the high flow/permeability group was **2.60 cm lower** (3.22 to 1.97 lower) than placebo	202 (3)	⊕⊕⊖⊖ LOW[3,4]
HD with haemoperfusion **VAS (0 to 10 cm)**	The mean VAS score of this control group was **0.6 cm lower** than pretreatment scores.	The mean reduction in VAS score of the HD with haemoperfusion group was **2.37 cm lower** (2.89 to 1.85 lower) than placebo	90 (1)	⊕⊕⊖⊖ LOW[1,3]
UV-B **Duo score,** **VAS, and %improvement**	The mean Duo score and VAS of this control group was **2.2 points and 0.3 cm lower** (respectively) than pretreatment scores.	The SMD of the UV-B group was **2.49 lower** (4.62 to 0.36 lower) than placebo	86 (4)	⊕⊕⊖⊖ LOW[1,3]
Thermal therapy **VAS (0 to 10 cm)**	The mean VAS score of this control group was **5.8 lower** than pretreatment scores.	The mean reduction in VAS score of the thermal therapy group was **2.06 lower** (6.98 lower to 2.84 higher) than placebo	41 (1)	⊕⊕⊖⊖ LOW[1,2]

The reduction of risk of pharmacological versus placebo (column 3) is the additional risk reduction in addition to the benefit provided by the placebo. "Lower" indicates a reduction or negative numerical change versus baseline.

CI: Confidence interval; **RR:** Risk Ratio; **SMD**: standardised mean difference; **VAS**: visual analogue scale

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Evidence of certainty was downgraded one level because of the reliance of the estimated effect on a small number of participants
[2]Evidence of certainty was downgraded one level because of the imprecise treatment estimate
[3]Evidence of certainty was downgraded one level because of study risks of bias
[4]Evidence of certainty was downgraded one level because heterogeneity between studies

BACKGROUND

Description of the condition

Itch (uraemic pruritus) is a common symptom in people with end-stage kidney disease (ESKD) and affects 42% to 57% of people on dialysis (Mistik 2006; Patel 2007; Pisoni 2006; Zucker 2003). Itch has significant adverse effects on quality of life (QoL) due to discomfort, disordered sleep, anxiety and depression (Narita 2006; Pisoni 2006). Despite its high prevalence, mechanisms driving uraemic itch remain poorly understood; two common theories implicate hyperactive and disordered immune (Mettang 2002) or opioid systems (Peer 1996). However, roles have also been proposed for hyperparathyroidism (Hampers 1968; Massry 1968), abnormal serum chemistry (Carmichael 1988), mast cell hyperactivity (Kaku 1990), and dialysis technique (Kato 2001; Tan 1991).

Description of the intervention

Itch has generally been used to refer to a symptom that is an intense sensation of the skin, either local or generalized, which triggers repeated scratching in an attempt to relieve the discomfort. Due to the commonality of itch in general, a formal definition in the context of chronic kidney disease (CKD) has been proposed (Zucker 2003). This defines uraemic itch as a) itch appearing shortly before the onset of dialysis, or at any time, without evidence of any other active disease that could explain the itch, b) three or more episodes of itch during a period of less than two weeks, with the symptom appearing a few times a day, lasting at least few minutes, and troubling the patient, and c) appearance of an itch in a regular pattern during a period of six months, but less frequently than listed above.

How the intervention might work

Given the variety of potential mediators in the pathophysiology of uraemic itch, a diverse range of interventions addressing the varied hypotheses has been investigated. These range from topical, symptomatic treatments to systemic treatments aimed at alleged underlying mechanisms. They largely target neurons (thought to be C-fibres transmitting to the posterior spinothalamic tract and onto the thalamus and somatosensory cortex), their receptors, or their various local inflammatory triggers in the skin. They are presented here by mechanism of action.

Opioid receptor mediation

Recent studies have recognised spinal Mu-receptor agonism as the mechanism of opioid-associated itch (Liu 2011), supporting the theory that uraemic itch could represent 'hyperactivity' of mu-receptors. A case report of successful treatment of uraemic itch with naloxone (Andersen 1984), a mu-receptor antagonist, appeared to supported this concept leading to the conduct of several trials to further define this effect (Pauli-Magnus 2000; Peer 1996). Mu agonism is typically associated with analgesia. Kappa agonism is typically associated with dysphoria and mu-antagonism. It has also been suggested that excessive mu-receptor or inadequate kappa-receptor activity, with systemic imbalance rather than isolated mu-receptor hyperactivity, may stimulate itch (Kumagai 2010). Thus, kappa-receptor agonism such a nalfurafine may also be a therapeutic target (Kumagai 2010; Wikstrom 2005a).

Anti-inflammatory immunomodulator mediation

A deregulated pro-inflammatory immune system has also been implicated in the development of uraemic itch. Histamine is the best-known immune trigger of pruritus. Preformed histamine is present in large amounts in mast cell granules. For this reason, after mast cell activation, it can be immediately released into the surrounding area where it can induce pruritus via H1 receptors on nerve fibres. Antihistamines act via prevention of the histamine fixation on the surface of the histamine receptors. Doxepin, a tricyclic antidepressant with anti-H1 receptor effect has been investigated with this presumed mechanism (Pour-Reza-Gholi 2007).

Increased mast cell numbers have been observed in the skin of patients with CKD (Dimkovic 1992; Matsumoto 1985) leading to speculation that this excess was associated with increased mast cell and histamine activity (Stockenhuber 1987). Antagonising histamine or inhibiting mast cell degranulation would block this pathway. Cromolyn sodium is a drug that blocks mast cell degranulation in response to antigens, leading to decreased release of histamine, leukotrienes, and other inflammatory mast cell products. Another purported mechanism of excessive mast cell degranulation is by relative zinc deficiency. By supplementing zinc, degranulation and histamine release may be prevented (Marone 1986). Leukotriene antagonists prevent the role of leukotrienes in sustaining the inflammatory response after degranulation.

The observation that sun exposure could relieve undifferentiated itch led to trials of ultraviolet radiation in uraemic itch (Gilchrest 1977; Ko 2011). Early positive results were eventually attributed to the effect of ultraviolet B radiation in altering T helper subsets (Garssen 1999). These conclusions led to several controlled and non-controlled trials of immunomodulators that could suppress T cell responses, such as tacrolimus, pimecrolimus, and thalidomide.

Thalidomide is a drug with anti-inflammatory properties by modification the immune systems The exact mechanism of action of thalidomide is unknown, but it inhibits TNF-α, IL-6, IL-10 and IL-12 and other pro-inflammatory cytokines. It modulates natural killer cell cytotoxicity and also inhibits NF-κB and COX-2 activity.

Nicotinamide (vitamin B3/niacin), and it is a member of the vitamin B family. It has no side-effects like its relative, nicotinic acid such as vasodilation or flushing, and it is considered generally safe as a food additive or as a component in cosmetics and medications (Narita 2006). Nicotinamide has been used for a diverse range of conditions, including acne, rosacea, autoimmune bullous dermatoses, photo-aging and photo immunosuppression by playing a significant role in DNA repair, maintenance of genomic stability and cellular response to injury, including inflammation and apoptosis (Cho 1997). It has been shown to be capable of inhibition of the expression of MHC-II and the production of IL-12, TNF-α and IL-1 and to be a potent stabilizer of mast cells and leukocytes (Namazi 2003).

Erythropoietin (EPO), a hormone produced by the kidneys that stimulates the production of red blood cells. The kidney synthetic function of EPO is impaired in CKD. EPO may have some anti-itch properties as it is has been shown to reduce plasma histamine concentrations (Bohlius 2009).

Turmeric, a powder of the rhizomes of Curcuma longa L. (Zingiberaceae), commonly used as a dietary spice, is also used in Asian and Iranian medicine ordinarily for treatment of inflammation and skin wounds (Baliga 2006). Curcumin (diferuloylmethane), the most active and non-toxic component of turmeric, is a polyphenol that has been extensively studied for its therapeutic benefits including anti- inflammatory activities (Aggarwal 2007).

Neuronal pathways

Gabapentin and pregabalin are structural analogues of the neurotransmitter gamma-aminobutyric acid (GABA). The exact mechanisms of their antipruritic effects are not clear but may be related to the hindrance of C-fibre mediated nociceptive sensations to the brain and thus pruritus (Patel 2007). Gabapentin may be particularly useful in forms of peripheral neuropathic pruritus, itch related to cholestasis, and post-burn itch in addition to uraemic itch (Rayner 2013).

Ondansetron is a 5-HT3 serotonin receptor antagonist to both the central and peripheral nervous system. 5-HT3 is known to be an activator of neuronal receptors along the C-fibre/spinothalamic pathway. The medication's possible efficacy in uraemic itch has been attributed to this mechanism (Yue 2015).

Capsaicin has been demonstrated to deplete substance P, a principal neurotransmitter regulating passage of noxious stimuli (Burks 1985), and may therefore block transmission of pruritic sensation.

Chilled baby oil can also interrupt the transmission of C nerve fibres and can minimize inflammation and chemical stimulation (Kennet 2007; Wang 2006). This is thought to be mediated by temperature induced vasoconstriction, reduced cell metabolism and nerve transmission speed, and paralysis of neural receptors (Chiu 2008).

Other interventions

Ergocalciferol is a precursor in the local production of active vitamin D in the skin of HD patients after exposure to sunlight. One hypothesis, supported by trials, claims anti-itch benefit from the positive effect of UVB exposure on uraemic pruritus (Shirazian 2013).

Activated charcoal is an agent that can bind many poisons in the stomach preventing them from being absorbed. Charcoal has been studied for possible effectiveness in uraemic pruritus (Giovannetti 1995).

Several agents have also been trialled on an empiric basis with identifiable mechanism. Cholestyramine and lidocaine have been trialled after published RCTs showed benefit with cholestatic itch (Villamil 2005). L-carnitine has been suspected as the causative agent in other symptoms of uraemia (Bohmer 1978). Pramoxine is a commercially available topical local anaesthetic that has been shown to have antipruritic properties when used both alone and in combination with lactic acid (Grove 2004). L-arginine ointment, a semi-essential amino acid, has been shown to improve skin dryness and, in particular, improve pruritus in haemodialysis (HD) patients (Durant-Finn 2008). Essential fatty acids and their derivatives have a protective function and influence skin structure and physiological characteristics (Andreassi 1997).

Why it is important to do this review

Itch affects the majority of CKD patients. The majority of patients on HD report itch symptoms. One fifth of all those on HD reported significant sleep disturbances (Narita 2006). Typically, trials investigating itch treatments are single centre studies with small numbers and often have conflicting results. The conclusions from past meta-analyses were that there was insufficient data to recommend one treatment compared with another, and further rigorous trials were needed. Therefore, it is important that a modern systematic assessment of the existing evidence be conducted to summarise the effect of current studies. The aim of this systematic review is to summarise randomised controlled trials (RCTs) in patients with ESKD comparing any topical or systemic intervention with placebo or usual care in the management of uraemic itch.

OBJECTIVES

Our objectives are to determine:

- the benefits and harms (both absolute and relative) of all topical and systemic interventions for the treatment of uraemic itch, either alone or in combination, when compared with placebo or standard care; and
- the dose strength or frequency, stage of kidney disease or method of dialysis used (where applicable) in cases where the effects of these interventions vary depending on co-interventions.

METHODS

Criteria for considering studies for this review

Types of studies

All RCTs and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) looking at evaluating interventions involving uraemic itch. Some studies allocated treatment based only on dialysis schedule (e.g. Monday, Wednesday, Friday) which also represent a systemic change in treatment and environment. These studies have not been included.

Types of participants

Inclusion criteria

Patients with advanced CKD defined as CKD stages 4, 5, or 5D were included.

Exclusion criteria

Patients with CKD stages 1, 2 and 3 were excluded. In studies before 2002, patients with CKD not on dialysis were excluded.

Types of interventions

All interventions, administered by any method (oral, intravenous (IV), topical, or otherwise), in any frequency and at any dose strength are included. Among people undergoing dialysis, the intervention may be administered on dialysis or non-dialysis days. Complementary interventions (such as acupuncture or massage) were excluded because they are not easily comparable or categorised with other interventions.

Participants in included study control arms received no intervention, placebo, a different dose strength or frequency from the experimental intervention, or any other intervention not administered to experimental arm participants.

We included studies of the type:

1. Intervention versus placebo
2. Intervention A versus intervention B
3. Co-intervention A versus co-intervention B.

To simplify interpretation, each intervention was assigned a GRADE evidence profile in a summary of findings table (Guyatt 2011).

Types of outcome measures

We assessed outcome measures at the end of the treatment period or up to two weeks post-treatment, or as reported by investigators.

Primary outcomes

- Post treatment itch
  - Measured by visual analogue scale (VAS), Duo score or any other validated score for itch
  - Other recognised numerical or categorical itch measurement scores.

Secondary outcomes

- QoL as measured by any validated QoL scale
- Death
- Length of treatment in hospital or outpatient clinic
- Length of time to itch relief
- Adverse events
  - Sleep disturbances
  - Dermatological reactions
  - Other adverse effects (e.g. neurological, gastrointestinal).

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Specialised Register up to 17 December 2019 through contact with the Information Specialist using search terms relevant to this review. The Cochrane Kidney and Transplant Specialised Register contains studies identified from several sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of kidney-related journals and the proceedings of major kidney conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney and transplant journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of search strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available on the Cochrane Kidney and Transplant website.

See Appendix 1 for search terms used in strategies for this review.

Searching other resources

- Reference lists of review articles, relevant studies, and clinical practice guidelines.
- Letters seeking information about unpublished or incomplete trials to investigators known to be involved in previous studies.
- Additional data sources included clinical study reports and direct correspondence with study authors.

Data collection and analysis

Selection of studies

The search strategy described was used to obtain titles and abstracts of studies that were potentially relevant to the review. Two authors independently screened titles and abstracts, and discarded studies that were not applicable; however, studies and reviews that potentially included relevant data or information on studies were initially retained. The two authors independently assessed retrieved abstracts and appropriate full texts of these studies to determine which studies satisfied our inclusion criteria.

Data extraction and management

Two authors carried out data extraction independently using standardised data extraction forms. Studies reported in non-English language journals were translated before assessment. The translators are noted in the acknowledgements. When more than one publication of one study exists, reports were grouped together and the publication with the most complete data was used in the analyses. When relevant outcomes are only published in earlier versions then these data were used. Any discrepancy between published versions were to be noted and there were no significant instances in this meta-analysis.

Assessment of risk of bias in included studies

The following items are independently assessed by two authors using the risk of bias assessment tool (Higgins 2011) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

For dichotomous outcomes (e.g. any itch versus no itch) results were expressed as risk ratios (RR) with 95% confidence intervals (CI). Where continuous scales of measurement were used to assess

the effects of treatment (e.g. Duo score or VAS), the mean difference (MD) was used, or the standardised mean difference (SMD) if different scales needed to be resolved.

Any validated tool for the quantification of itch was used. These included, but were not limited, to VAS and the Duo scoring system, which were the most commonly reported measurement tools for itch. VAS was scored on a 10-point scale and the Duo scoring system is based on severity, distribution, and sleep disturbance up to a maximum score (usually 45). RCTs with clearly documented, but non-validated scoring systems were considered as non-ideal evidence.

Unit of analysis issues

The unit of focus was the quantities and qualities affecting a single person. For example, itch episodes/person was preferable to total number of itch episodes affecting an unspecified number of people or time frame.

Dealing with missing data

Further information required from the original author was requested by written correspondence (e.g. emailing corresponding author/s) and any relevant information obtained in this manner was included in the review. Evaluation of important numerical data such as screened, randomised patients as well as intention-to-treat, as-treated and per-protocol population were to be performed. Attrition rates, for example drop-outs, losses to follow-up and withdrawals were investigated.

For missing data of the second stage of a cross-over RCT, assuming appropriate data can be acquired from the first (pre-cross-over) stage, the second stage was dropped from the analysis. The "first" stage was treated at as a parallel RCT. When all the means and SD for both groups and both periods were available with an incomplete paired data analysis, all measurements from both periods were treated as parallel group studies. If this analysis in consistent with the data provided within the study, we accepted this with the acknowledgement of risk of bias in both the inflation of confidence intervals and study heterogeneity. Finally, if paired data were available (or able to be fully reconstructed) then the generic inverse variance method was used to incorporate the studies into the meta-analysis.

Issues of missing data and imputation methods (for example, last-observation-carried-forward) was critically appraised (Higgins 2011).

Assessment of heterogeneity

Heterogeneity was analysed using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test (Higgins 2003). I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

Assessment of reporting biases

Given the size and organisation of participants in this review, funnel plots (used to assess for the potential existence of small study bias) were not included. Reporting bias was discussed on an individual study basis (Characteristics of included studies).

Data synthesis

Data was pooled using the random-effects model.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was used to explore possible sources of heterogeneity (e.g. participants, interventions, and study quality). Heterogeneity among participants could be related to age, geography, and stage of CKD. Heterogeneity in treatments could be related to prior agent(s) used and the agent, dose, and duration of therapy (such as increased tolerance after prolonged use of anti-itch agents). Additionally, cross-over studies may represent an independent source of bias due to their paired design. Adverse effects have been tabulated and assessed using descriptive techniques, because they are likely to differ among agents used. We planned to calculate the 95% risk difference for each adverse effect. However, due to the variety of interventions used and the inadequate reporting of adverse events, this was not done.

Sensitivity analysis

We planned to undertake sensitivity analyses however due the wide variety of interventions this was not performed.

Summary of findings' tables

We have presented the main results of the review in 'Summary of findings' tables. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schunemann 2011a). The 'Summary of findings' tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach (GRADE 2008; Guyatt 2008). The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Schunemann 2011b). We presented the following outcomes in the 'Summary of findings' tables.

- Itch severity: a patient's subjective rating of their sensation of itch. Severity is measured on a continuous scale or as a binary response. The most common itch scales included were the VAS and Duo score. Few studies included their own holistic scale based on varying degrees of validated evidence.
- VAS: a 0 to 10 cm rating using the horizontal or vertical numeric rating scale for subjective characteristics or attitudes that cannot be directly measured. It was developed originally to assess the intensity of pain, but subsequently it was also adopted for pruritus evaluation. A number of studies dealing with itch have demonstrated that VAS is a reliable method of pruritus severity measurement (Reich 2012)
- Duo score: a numerical measure of itching scoring according to severity, frequency, and distribution with roughly equal contributions from each category. Originally proposed by Duo 1987, modified by Mettang 1990, and again by (Hiroshige 1995), the structure has remained consistent, while the range of score has varied from 0 to 10 to 3 to 81.
- Adverse events: adverse effects were poorly and inconsistently reported across all studies. These have been documented in the results section and 'additional tables' (Table 1; Table 2; Table 3; Table 4; Table 5). Further meaningful assessments on harm

could not be made and were not included in the 'Summary of findings' tables.

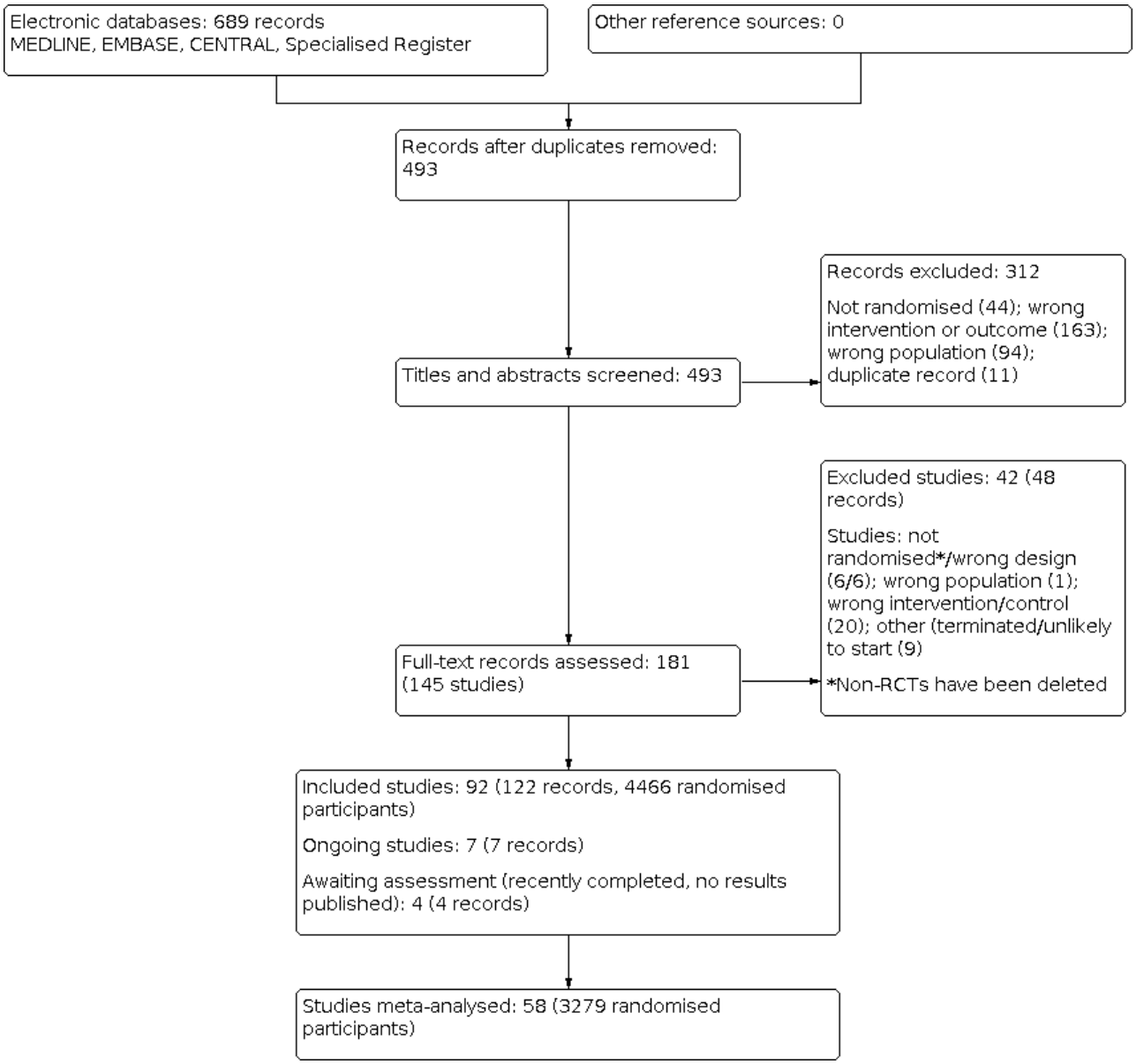
RESULTS

Description of studies

Results of the search

The process of selecting records and studies for inclusion in this systematic review is outlined in Figure 1. The titles, abstracts, and summaries of 689 records were evaluated from three separate databases and the Specialised Register. Overlap within the database searches resulted in 196 records removed as duplicate records. An additional 312 records were excluded due to failing to meet study design, intervention, participant, or outcome criteria prior to full-text review.

Figure 1. Study flow diagram.



We contacted 27 authors of papers with conflicting or missing data. Of all authors contacted for further clarification seven responded including Dr. Tol, Dr. Ashmore, Dr. Tarng, Dr. Pornanong Aramwit. Dr. Fleicher, Dr. Peer, and Dr. Haghverdi. Five authors provided supplementary data incorporated into the review.

In total we identified 144 studies (181 records). Ninety-one studies met our inclusion criteria and 42 studies (48 records) were excluded; six non-RCTs were subsequently deleted. There are seven ongoing studies (ACTRN12614000677606; DON'T ITCH 2015; IRCT201311152417N14; IRCT2015051411940N3; NCT03422653; NCT03636269; SNUG 2019 and three studies (NCT01513161;

NCT02696499; NCT02747979) have recently been completed but have yet to report results. These 10 studies will be assessed in a future update of this review.

Included studies

Ninety-two studies (122 records) randomising 4466 participants met our inclusion criteria. All were RCTs that evaluated changes in itch (the primary outcome) associated with CKD before and after an intervention. Almost 90% of all RCTs originated from the USA, UK, Israel, Taiwan, Iran, Germany, or Japan. Translated non-English study languages included Farsi, French, Mandarin, Turkish, German, and Spanish.

The identified RCTs yielded a broad spectrum of different interventions for the treatment of itch associated with different underlying diseases. A total of 78 studies were placebo-controlled, five studies compared gabapentinoids versus antihistamines or gabapentin versus pregabalin, and nine studies compared different dialysis modalities or dialysis solutions.

The most common reason for studies not to be included in this review's quantitative analysis was inadequate reporting that precluded a meaningful comparison (e.g. SD or placebo results not explicitly reported). Thirty additional studies were included in the qualitative analysis.

All but 23 studies described adverse effects in at least the intervention group. Just over half of the studies failed to specify adverse effects (or lack thereof) in the control population. A handful of studies also measured QoL, sleep quality, depression, dialysis quality, or patient satisfaction. Two studies with pharmacological interventions measured the interaction of dialysis modality with their intervention. No meaningful qualitative or quantitative analysis could be made from secondary outcomes other than adverse events.

For additional information on all included studies see Characteristics of included studies.

Excluded studies

Forty-two studies were excluded from this review after comprehensive full text analysis. The most common reasons for exclusion were not meeting proper criteria for a true RCT, followed by inappropriate intervention. Four studies did not meet our protocol's criteria for the target population. Finally, eight excluded studies appeared to have never been initiated or stopped prematurely without publishing results.

Across all searched studies the most common reasons for exclusion were:

1. Outcome not truly itch-related (e.g. serum PTH level used as a surrogate monitor)
2. Lack of a true control, self-control, or comparison group
3. Wrong intervention
4. Selected studies were not truly randomised or pseudo-randomised.
5. Gross omission of data based on the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011).
6. Selected studies include patients without CKD
7. Study was never initiated or stopped prematurely without publishing results.

For additional information on all excluded studies see Characteristics of excluded studies

Risk of bias in included studies

All studies included in the meta-analyses were RCTs, either parallel or cross-over. Each explicitly reported patients as randomised to an intervention or placebo group. Sensitivity analyses were conducted for each intervention that included both only parallel RCTs versus cross-over with parallel RCT data. No significant differences in effect size of heterogeneity were observed. See Figure 2; Figure 3.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

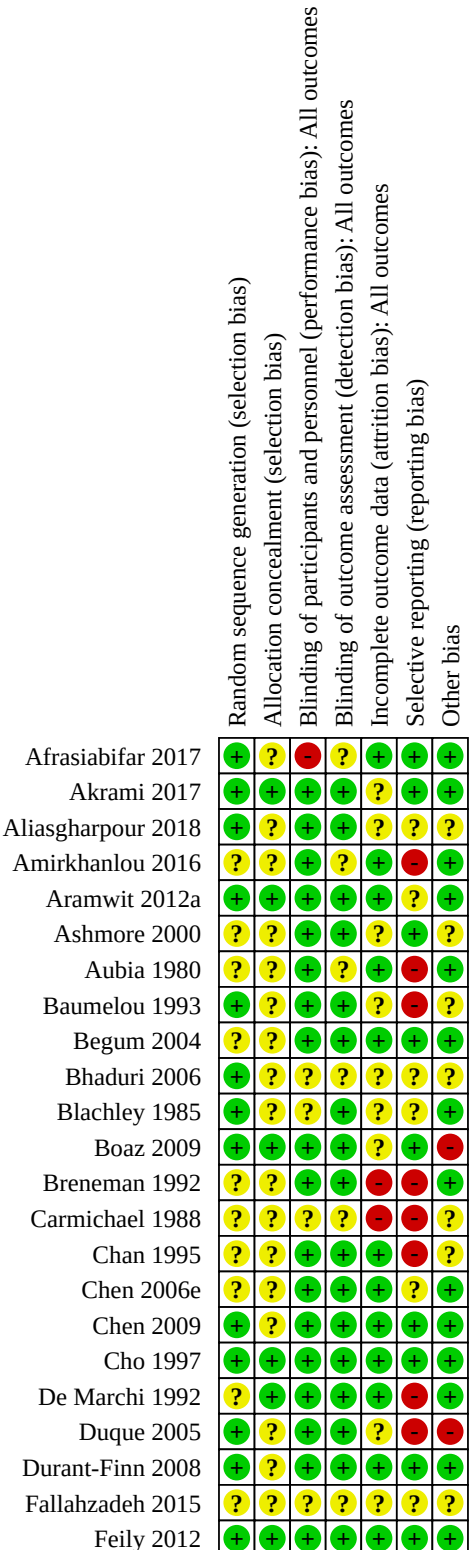


Figure 2. (Continued)

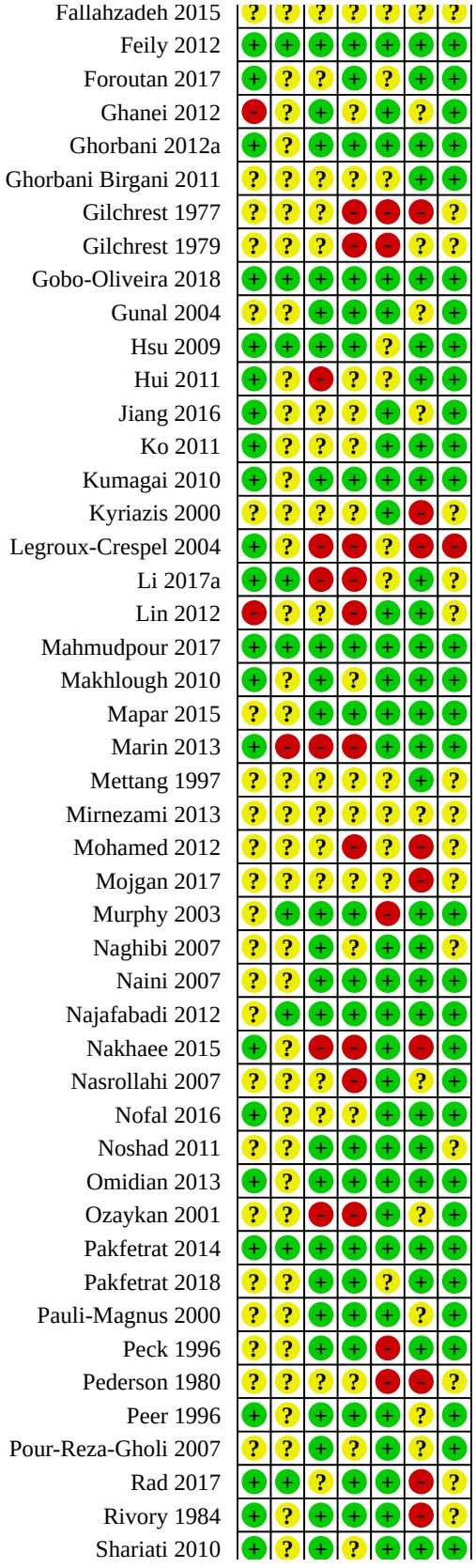


Figure 2. (Continued)

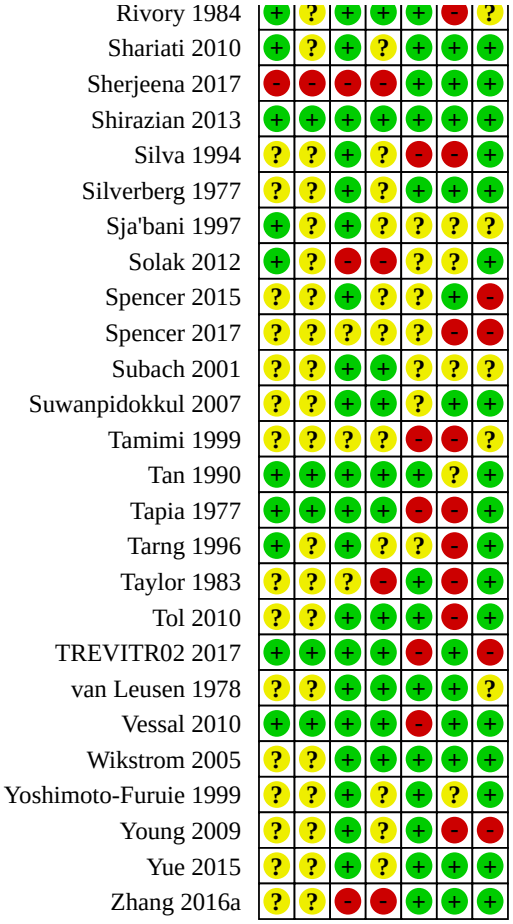
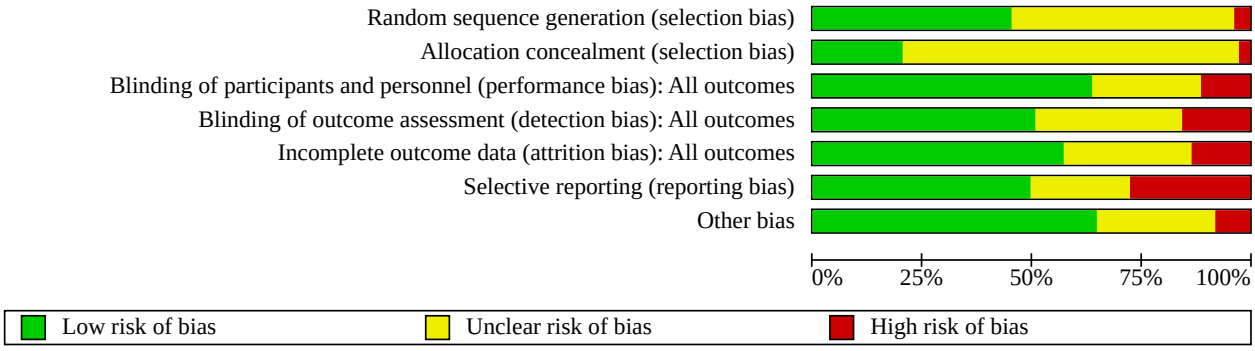


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Random sequence generation

Forty-two studies reported a specific method of randomisation, either computer-generated or the use of a random number table. Three studies were judged to be at high risk of bias (Ghanei 2012; Lin 2012; Sherjeena 2017), and the remaining 47 studies were considered to be uncertain risk.

Allocation concealment

Nineteen studies were judged to be al low risk of bias for allocation concealment, two were at high risk of bias ((Marin 2013; Sherjeena

2017), and the remaining 71 studies were considered to be of uncertain risk.

Blinding

Two studies (Ko 2011; Nasrollahi 2007) only blinded the participants (single blind), and three studies (Lin 2012; Marin 2013; Ozaykan 2001) were open-label studies. Complicated equipment for emitting UVB radiation (Ko 2011; Sherjeena 2017), administering new dialysis modalities (Zhang 2016a), or the absolute temperature of the intervention (Lin 2012; Rad 2017) may have precluded any blinding efforts. The majority of blinded studies utilized unlabelled pills/infusions for oral/IV interventions or a comparable unlabelled vehicle of similar consistency for blinding of a topical agent.

For performance bias, 10 studies were judged to be at high risk of bias (Afrasiabifar 2017; Hui 2011; Legroux-Crespel 2004; Li 2017a; Marin 2013; Nakhaee 2015; Ozaykan 2001; Sherjeena 2017; Solak 2012; Zhang 2016a), 59 studies were at low risk of bias, and the remaining 23 studies were considered to be of uncertain risk.

For detection bias, 14 studies were judged to be at high risk of bias (Gilchrest 1977; Gilchrest 1979; Legroux-Crespel 2004; Li 2017a; Lin 2012; Marin 2013; Mohamed 2012; Nakhaee 2015; Nasrollahi 2007; Ozaykan 2001; Sherjeena 2017; Solak 2012; Taylor 1983; Zhang 2016a), 47 were at low risk of bias, and the remaining 30 studies were considered to be of uncertain risk.

Incomplete outcome data

Eight studies (Carmichael 1988; Gilchrest 1979; Murphy 2003; Peck 1996; Pederson 1980; Silva 1994; Tapia 1977; Vessal 2010) had a greater than 10% dropout rate, mainly reflective of low sample sizes. The average post randomisation size of these eight studies was 28 participants. Only one of these studies analysed on an intention-to-treat basis. Twenty-two of the remaining studies were completed with one or more dropouts after randomisation; half were analysed on an intention-to-treat basis.

For attrition bias, 12 studies were judged to be at high risk of bias (Breneman 1992; Carmichael 1988; Gilchrest 1977; Gilchrest 1979; Murphy 2003; Peck 1996; Pederson 1980; Silva 1994; Tamimi 1999; Tapia 1977; Vessal 2010), 52 studies were at low risk of bias, and 28 studies were considered to be of uncertain risk.

Selective reporting

Two studies appeared to only report and collect categorical or binary endpoints such as “significant itch reduction” versus “no significant itch reduction (Gilchrest 1979; Tapia 1977). Silva 1994 clearly collected continuous itch outcomes, but only reported and analysed binomial outcomes. Tol 2010, Pederson 1980, and Tarng 1996 did not report placebo results and could not be included in the quantitative analysis.

For reporting bias, 25 studies were judged to be at high risk of reporting bias (Amirkhanlou 2016; Aubia 1980; Baumelou 1993; Breneman 1992; Carmichael 1988; Chan 1995; De Marchi 1992; Duque 2005; Gilchrest 1977; Kyriazis 2000; Legroux-Crespel 2004; Mohamed 2012; Mojgan 2017; Nakhaee 2015; Pederson 1980; Rad 2017; Rivory 1984; Silva 1994; Spencer 2017; Tamimi 1999; Tapia 1977; Tarng 1996; Taylor 1983; Tol 2010; Young 2009), 46 studies were at low risk of bias, and 21 studies were considered to be of uncertain risk.

Other potential sources of bias

In all the included studies, post-randomisation dropout rates were balanced (no statistically significant difference in dropout rates) between intervention and control with the exception of Pauli-Magnus 2000 which had five dropouts (2.5%) in the intervention group for the indication of opioid pain relief. However, this was anticipated in pretrial planning and the patients were included in the analysis on an intention-to-treat basis.

The authors of six studies (Boaz 2009; Duque 2005; Spencer 2015; Spencer 2017; TREVITR02 2017; Young 2009) had financial backing from the respective pharmaceutical manufacturers. One study (Legroux-Crespel 2004) reported conflicting results and used arbitrary definitions of improvement. These seven studies were judged to be at high risk of bias. Sixty studies were judged to be at low risk of bias and 25 studies were considered to of uncertain risk.

Effects of interventions

See: **Summary of findings 1** Pharmacological interventions versus placebo for the relief of itch in people with advanced chronic kidney disease; **Summary of findings 2** Topical treatments versus placebo for the relief of itch in people with advanced chronic kidney disease; **Summary of findings 3** Supplements, haemodialysis modalities, and other treatments for the relief of itch in people with advanced chronic kidney disease

We organised the studies into the following groups:

1. Pharmacological interventions
2. Topical interventions
3. Oral or IV supplements
4. Dialysis modality
5. All other interventions.

1. Pharmacological interventions

See Summary of findings 1; adverse effects Table 1.

GABA analogues

Twelve studies (Amirkhanlou 2016; Foroutan 2017; Gobo-Oliveira 2018; Gunal 2004; Marin 2013; Naghibi 2007; Naini 2007; Nofal 2016; Noshad 2011; Solak 2012; Tol 2010; Yue 2015) involving 618 patients and 13 comparisons, investigating the effects of either oral gabapentin or pregabalin. Dosing included 300 mg twice weekly oral gabapentin (Gunal 2004; Nofal 2016), 400 mg of twice weekly oral gabapentin (Naini 2007) or 75 mg twice weekly oral pregabalin (Yue 2015) compared to placebo. Naghibi 2007 did not explicitly state the dose of gabapentin. These five studies all reported itch on a 10 cm VAS.

GABA analogues versus placebo

GABA analogues reduced symptoms of uraemic itch compared to placebo (Analysis 1.1.1 (5 studies, 297 participants): MD -4.95 cm, 95% CI -5.46 to -4.44 on VAS; I^2 = 0%; high certainty evidence). The overall certainty of the evidence was high as these results were taken from multiple RCTs with large, homogeneous magnitudes of effect and narrow (%% CI demonstrating precision and efficacy. Risk of bias was uncommon and low overall.

Tol 2010, a placebo controlled cross-over RCT involving 14 patients taking gabapentin 300 mg/HD session, did not report placebo

results and could not be included in the quantitative analysis. Tol 2010 reported a significant absolute reduction in itch during gabapentin treatment: 6.3 cm (95% CI 3.8 to 8.8) versus baseline in VAS similar to the other gabapentin studies.

GABA analogues versus antihistamines

Five studies examined the efficacy of gabapentin versus various antihistamines. Marin 2013 compared 300 mg gabapentin every two days versus 10 mg oral loratidine every two days; Noshad 2011 studied 100 to 200 gabapentin mg/day versus oral hydroxyzine; Amirkhanlou 2016 measured a binary response of itch improvement from gabapentin versus oral ketotifen; Gobo-Oliveira 2018 compared 300 mg gabapentin 3 times/week versus 6 mg oral dexchlorpheniramine twice/day; and Suwanpidokkul 2007 studied 100 mg gabapentin/day versus 10 mg loratidine/day. Overall, GABA analogues (gabapentin) may reduce symptoms of uraemic itch (Analysis 1.1.2 (5 studies, 220 participants): SMD 0.44 reduction, 95% CI 0.75 to 0.14 lower; I^2 = 22%; low certainty evidence) compared to antihistamines.

While these are four separate independent RCTs, there was low to moderate heterogeneity (the efficacy of oral antihistamines was highly variable), and two studies are at high risk of bias. Amirkhanlou 2016 does not report baseline scores and Marin 2013 was an open-label study.

Yue 2015 (in addition to the placebo comparison above) reported a relative reduction of 4.1 cm (95% CI 1.98 to 6.22) with pregabalin over ondansetron. Solak 2012 compared 300 mg gabapentin/day to 75 mg pregabalin/day and reported no significant difference in itch reduction between the two treatments.

Adverse effects

Across the studies, few mild adverse effects occurred. Somnolence, dizziness, and fatigue are reported in less than 5% of patients in the intervention groups. No moderate or severe adverse effects are reported.

Ondansetron

Ondansetron versus placebo

Three studies (Ashmore 2000; Murphy 2003; Yue 2015) investigated the effects of 8 mg oral ondansetron 3 times/day. All three studies reported itch on a 10 cm VAS, however Ashmore 2000 employed a cross-over design and reported VAS with only medians and interquartile ranges. This analysis extrapolates means and SDs according to the standard practice recommendations of Cochrane. Based on the inherent variability of these changes, a sensitivity analysis of ondansetron interventions without Ashmore 2000 was performed.

Ondansetron did not reduce symptoms of uraemic itch (Analysis 1.1.3 (3 studies, 183 participants): MD -0.38 cm, 95% CI -1.04 to 0.27 on VAS; high certainty evidence) compared to placebo. These finding remain valid with the exclusion of Ashmore 2000. The placebo group experienced a non-significant mean decrease in VAS ranging from 0.1 to 2 cm.

Ondansetron versus antihistamine

Ozaykan 2001 compared ondansetron to the antihistamine cyproheptadine. The authors report a slight improvement in itch reduction with ondansetron compared to cyproheptadine.

Subach 2001 and Mirnezami 2013 compared ondansetron to diphenhydramine and loratidine, respectively. Neither study found any difference in measured itch.

Adverse effects

Nausea and vomiting were reported as uncommon and mild in severity.

Kappa-opioid agonists versus placebo

Six studies investigated the effects of either 5 µg/day or 2.5 µg/day nalfurafine (oral or IV) (Bhaduri 2006; Kumagai 2010; Wikstrom 2005 (1); Wikstrom 2005 (2)) and a newly synthesized agent "CR845" (Spencer 2015; Spencer 2017) at 0.5, 1.0, and 1.5 µg/kg IV with dialysis. All studies reported itch on a 10 cm VAS.

Kappa opioid agonists reduced symptoms of uraemic itch (Analysis 1.1.4 (5 studies, 661 participants): MD -1.05 cm, 95% CI -1.40 to -0.71 on VAS; I^2 = 0%; high certainty evidence). Bhaduri 2006 reported no decrease in itch on VAS.

Both studies examining CR845 were funded by Cara Therapeutics and were judged to be at high risk of bias. A sensitivity analysis without the CR845 studies yields the similar result. The additional power from these two high risk studies are not required to maintain the high certainty of the evidence.

Adverse effects

Adverse effects were common and were mild to moderate in severity. Somnolence, headache, insomnia, diarrhoea, and nausea/vomiting were reported in 2% to 10% of the intervention group.

Mu opioid antagonists versus placebo

Two cross-over studies (Pauli-Magnus 2000; Peer 1996) compared 50 mg naltrexone once/day with placebo. Both studies evaluated itch on a 10 cm VAS.

Mu opioid antagonists may not improve symptoms of uraemic itch (Analysis 1.1.5 (2 studies, 62 participants): MD -4.29 cm, 95% CI -10.24 to 1.66 on VAS; low certainty evidence).

Pauli-Magnus 2000 reported interquartile ranges and Peer 1996 reported only percentage changes of VAS. Results are merged according to the standard practice recommendations of Cochrane. Additionally, Peer 1996 evaluated the effect of naltrexone on uraemic itch using Duo scale as well as VAS. There was no significant difference reported between naltrexone and placebo in these studies.

Adverse effects

These studies found that the adverse effects of Mu opioid antagonists are both somewhat common and mild to moderate in severity. Symptoms reported included loss of appetite, nausea, heartburn, and other gastrointestinal symptoms in approximately one third of the intervention groups. In addition, patients ceased any opioid medication for the duration of the trial period. Acute pain management became a common reason for cessation of natrexone during the studies resulting in many dropouts post randomisation.

Nalbuphine versus placebo

TREVITR02 2017 compared nalbuphine, a combined kappa-opioid agonist and mu-opioid antagonist, to placebo. Nalbuphine may make little or no difference to uraemic itch (Analysis 1.1.6 (1 study, 179 participants): MD -0.75 cm, 95% CI -1.70 to 0.20 on VAS; low certainty evidence).

This study did not report on adverse effects.

Cromolyn versus placebo

Vessal 2010 reported oral cromolyn may reduce symptoms of uraemic itch compared to placebo (Analysis 1.1.7 (1 study, 40 participants): MD -4.8 cm, 95% CI -7.03 to- 2.57; low certainty evidence).

Adverse effects

The adverse effects reported were flatulence in one patient in the cromolyn group and three gastrointestinal complaints in the placebo group.

Nicotinamide versus placebo

A four-week study by Omidian 2013 evaluated nicotinamide versus placebo. Nicotinamide may make little or no difference to the symptoms of uraemic itch (Analysis 1.1.8 (1 study, 50 participants): 0.47 cm, 95% CI -0.32 to 1.26; low certainty evidence).

No adverse effects were reported in either the nicotinamide to placebo groups.

Erythropoietin versus placebo

A four-week study by De Marchi 1992 evaluated erythropoietin versus placebo. Erythropoietin had uncertain effects on the symptoms of uraemic itch (Analysis 1.1.9 (1 study, 29 participants): MD -14.50, 95% CI -38.78 to 9.78 on 40 point Duo score; very low certainty evidence).

Sja'bani 1997 reported that the erythropoietin group experienced a significantly greater mean reduction in itch than the placebo group. However, baseline itch scores are not fully reported to allow for inclusion in the quantitative review.

These studies did not report on adverse effects.

Cholestyramine versus placebo

Two cross-over studies (Silverberg 1977; van Leusen 1978) compared cholestyramine and placebo. Cholestyramine may make little or no difference to the symptoms of uraemic itch (Analysis 1.1.10 (2 studies, 15 participants): MD 0.00, 95% CI -0.49 to 0.49 on a 0 to 3 severity scale; low certainty evidence).

These studies did not report on adverse effects.

Montelukast versus placebo

One cross-over study (Nasrollahi 2007) and one parallel study (Mahmudpour 2017) compared montelukast to placebo. Duo score and VAS were measured, respectively.

Montelukast may slightly reduce symptoms of uraemic itch (Analysis 1.1.11 (2 studies, 87 participants): SMD -1.40, 95% CI -1.87 to -0.92; moderate certainty evidence).

Homogeneity was difficult to assess as the RCTs used well validated but slightly different itch severity scores.

Adverse effects

One patient in the intervention group of Nasrollahi 2007 developed myelodysplastic syndrome, but this was not considered an adverse effect of Montelukast. In comparison, one patient in the placebo first group developed a myocardial infarction prior to being allocated to Montelukast. No other adverse effects were reported.

Sertraline versus placebo

Pakfetrat 2018 compared sertraline and placebo. Sertraline may make little or no difference to the symptoms of uraemic itch (Analysis 1.1.12 (1 study, 46 participants): MD -1.80 cm, 95% CI -3.65 to 0.05 on VAS; low certainty evidence).

This study did not report on adverse effects.

Lidocaine versus placebo

Tapia 1977 compared 600 mg IV lidocaine once/day and placebo. Only acute (15 to 30 minutes) relief of pruritus was included in the analysis. It is unclear whether lidocaine relieved itch (within 30 minutes) compared to placebo due to very low certainty evidence (Analysis 1.1.13 (1 study, 16 participants): MD -0.63 cm, 95% CI -1.46 to 0.19). Longer term assessment was not reported. Improvement in itch was reported in 8/10 participants receiving lidocaine and 1/6 participants receiving placebo (Analysis 1.2.1); the definition of improvement was not reported.

This study did not report on adverse effects.

Thalidomide versus placebo

Silva 1994 compared 100 mg thalidomide/day for one week with placebo. Thalidomide may relieve itch following administration (Analysis 1.2.2 (1 study, 18 participants): RR 4.17, 95% CI 1.08 to 16.15) compared to placebo, however, the certainty of the evidence was very low as these results were taken from a single study with a small number of participants, and a high number of dropouts (11).

No adverse effects were reported in either the placebo or thalidomide groups.

Sodium thiosulfate versus placebo

Mohamed 2012compared 12.5 mg sodium thiosulfate/dialysis session and placebo. Overall, there was no reported significant difference comparing sodium thiosulfate and placebo. The study was not included in the quantitative analysis due to incomplete reporting of results.

The study did not report on adverse effects.

Doxepin versus placebo

Pour-Reza-Gholi 2007 compared 10 mg doxepin twice/day and placebo in a cross-over study. Complete improvement was achieved in 58% of participants on doxepin which was significantly higher than placebo (P > 0.001).

Adverse effects

Mild drowsiness was a commonly reported complaint and resulted in one dropout. Placebo adverse effects were not reported.

Antihistamines

Aubia 1980compared 400 mg oral cimetidine once/day (over and up to 1 hour), a different unspecified "classical antihistamine", and placebo. The study found no significant differences between the three groups. No measures of variability (e.g. standard error) were reported.

Antihistamines were compared with four other interventions: ondansetron, topically applied dilute vinegar, GABA agonists (gabapentin; see above section on GABA analogues), and Mu opioid antagonists (naltrexone).

- Ozaykan 2001 reported the ondansetron group experienced a significantly greater mean reduction: 9 point (95% CI 16.34 to 1.64) compared to cyproheptadine (first generation antihistamine) using Duo pruritus score.
- Nakhaee 2015 reported no significant difference between hydroxyzine and topically applied dilute vinegar.
- Legroux-Crespel 2004 reported no significant difference between loratidine and the Mu opioid antagonist naltrexone.
- Baumelou 1993 reported no significant difference between the two antihistamines cetirizine and dexchlorpheniramine. However, both significantly improved itch compared to placebo.

Other therapies

Several isolated interventions could not be included in the quantitative analysis due to insufficient reporting of results.

- Fallahzadeh 2015 reported a significant improvement with oral senna compared to placebo in patients with uraemic pruritus.
- Pederson 1980reported a significant reduction with oral charcoal compared to placebo.
- Rivory 1984 reported a significant improvement in itch with nicergoline compared to placebo.
- Shariati 2010 reported oral charcoal was significantly more effective in reducing VAS in patients with uraemic pruritus than oral aluminium hydroxide.

2. Topical interventions

See Summary of findings 2; adverse effects Table 2.

Capsaicin cream versus vehicle cream

Three studies tested the efficacy of the topical agent capsaicin in treating CKD-related uraemic pruritus: 0.025% (Cho 1997) or 0.03% (Makhlough 2010; Tarng 1996) capsaicin cream applied 4 times/day versus vehicle cream (placebo). Evaluation of itch was reported on a 10 cm VAS and a customized 4-point itch scale (Makhlough 2010). Capsaicin cream application probably reduced the symptoms of uraemic itch (Analysis 2.1.1 (2 studies, 112 participants): SMD -0.84, 95% CI -1.22 to -0.45; I^2 = 0%; moderate certainty evidence) than during the vehicle application period.

Tarng 1996 did not provide any results for the placebo cross-over periods and could not be included in the quantitative analysis. Within the intervention group of that study, approximately 80% of patients initially reported moderate to severe pruritus and then none or mild symptoms post-intervention.

Adverse effects

All studies reported mild local burning sensations and cutaneous erythema as adverse effects.

Pramoxine cream versus vehicle cream

Young 2009) compared 1% pramoxine cream twice/day with vehicle cream. It is uncertain whether pramoxine cream decreased uraemic itch (Analysis 2.1.2 (1 study, 28 participants): MD -1.97 cm, 95% CI -6.06 to 2.12; very low certainty evidence) compared to vehicle.

This study did not report on adverse effects.

Calcineurin inhibitor cream versus vehicle cream

Two studies compared 0.1% tacrolimus (Duque 2005) and 1% pimecrolimus (Ghorbani 2012a) with vehicle cream. Duque 2005 did not report SD (or any measurement of variability/error) and was not included in the quantitative analysis. Duque 2005 reported pimecrolimus cream application resulted in a non-significant, but greater reduction in VAS compared to the vehicle cream.

It is uncertain whether 1% pimecrolimus reduced uraemic itch (Analysis 2.1.3 (1 study, 60 participants): MD 1.2 cm, 95% CI -0.36 to 2.76; very low certainty evidence) compared to vehicle.

Adverse effects

Adverse effects of the tacrolimus cream included a burning sensation over the area of skin applied with cream.

Dead Sea lotion versus vehicle lotion

Boaz 2009 compared Dead Sea lotion, containing Dead Sea water and sea silt (Dead Sea mud), and two related vehicle lotion groups. Itch was quantified using a 5-point itch severity scale. It is uncertain whether Dead Sea lotion reduced uraemic itch (Analysis 2.1.4 (1 study, 41 participants): MD -2.00, 95% CI -4.31 to 0.31 on 5-point severity scale; very low certainty evidence) compared to vehicle.

This study did not report on adverse effects.

Cromolyn cream

Cromolyn cream versus vehicle cream

Feily 2012 compared 4% cromolyn cream twice/day and vehicle cream. Cromolyn cream may not reduce uraemic itch (Analysis 2.1.5 (1 study, 60 participants): MD 0.8 cm, 95% CI -1.98 to 0.38; low certainty evidence) compared to vehicle.

This study did not report on adverse effects.

Cromolyn cream versus calcineurin inhibitor cream

Ghorbani Birgani 2011 compared 4% cromolyn cream with 1% pimecrolimus cream. This study reported both interventions significantly reduced pruritus on a VAS with a non-significant difference between the two.

Sericin cream versus vehicle cream

Aramwit 2012a compared sericin cream and vehicle cream. Itch was reported on a 10 cm VAS. This study reported the sericin cream group experienced a significant absolute mean decrease in itch: 2.8 cm reduction (95% CI 0.5 lower to 5.1 lower) in VAS. Placebo results were not reported and the study could not be included in the quantitative analysis.

This study did not report on adverse effects.

Baby oil versus placebo

Lin 2012 compared chilled and unchilled baby oil with a common vehicle. Itch was evaluated on with a customized 21-point itch severity scale that incorporated itching, dryness, peeling, tightness, and sleep disturbances. The itch severity scale does not appear to be well validated unlike VAS or Duo score. The placebo group experienced a 1-point non-significant decrease in itch severity scale.

Overall, baby oil application may reduce uraemic itch (Analysis 2.1.6 (1 study, 93 participants): MD -2.38, 95% CI -3.49 to -1.27; low certainty evidence) compared to vehicle.

The report documented that no adverse effects occurred using either intervention or vehicle.

L-arginine versus vehicle salve

Durant-Finn 2008compared L-arginine salve and vehicle salve groups. Itch was quantified using a 3-point itch severity scale. L-arginine may make little or no difference to uraemic itch (Analysis 2.1.7 (1 study, 48 participants): MD -0.58, 95% CI -1.86 to 0.7 on 3-point severity scale; low certainty evidence) compared to vehicle.

This study did not report on adverse effects.

Polyunsaturated fatty acids versus vehicle cream

Chen 2006e and Afrasiabifar 2017 compared topically applied polyunsaturated fatty acids of varying concentrations and quantity with vehicle cream. Itch was reported with a 10 cm VAS in both studies.

Topically applied polyunsaturated fatty acids may make little or no difference to uraemic itch (Analysis 2.1.8 (2 studies, 78 participants): SMD -0.91, 95% CI -1.99 to 0.17; I^2 = 88% low certainty evidence) compared to vehicle.

These studies did not report on adverse effects.

Eurax cream versus Sarna lotion

Tan 1990 compared Eurax cream with Sarna lotion and reported a statistically significant reduction of uraemic itch for both the Eurax cream and Sarna lotion periods.

This study did not report on adverse effects.

3. Oral or IV supplements

See Summary of findings 3; adverse effects Table 3.

Oral polyunsaturated fatty acids versus placebo

Three studies (Ghanei 2012; Peck 1996; Yoshimoto-Furuie 1999) tested the efficacy of 1 g polyunsaturated fatty acids 3 time/day versus placebo. Itch was evaluated with a customized 5-point itch scale with continuous or binary results reported. Only Ghanei 2012 also reported complete placebo results.

Ghanei 2012 reported oral polyunsaturated fatty acids may decrease uraemic itch (Analysis 3.1.1 (1 study, 22 participants): MD -11.30%, 95% CI -19.01% to -3.59%; low certainty evidence) compared to placebo. Two additional studies (Peck 1996; Yoshimoto-Furuie 1999) also reported reductions in itch scores versus baseline, but did not include sufficient reporting of placebo results.

Mojgan 2017 examined fish oil supplements versus placebo and reported a small but significant benefit versus placebo; neither CIs nor SDs were reported.

Begum 2004 compared fish oil and safflower oil (both polyunsaturated fatty acids) and found neither significantly reduced itch on a VAS.

These studies did not report on adverse effects.

IV L-carnitine versus placebo

Mettang 1997 compared 10 mg IV L-carnitine/kg and IV placebo once/dialysis session. Evaluation of itch used a 10 cm VAS. IV L-carnitine may make little or no difference to uraemic itch (Analysis 3.1.2 (1 study, 12 participants): MD -0.26 cm, 95% CI -2.85 to 2.43 on VAS; low certainty evidence) compared to IV placebo.

This study did not report on adverse effects.

Oral zinc sulfate versus placebo

Two studies (Mapar 2015; Najafabadi 2012) compared 220 mg oral zinc sulfate twice/day and placebo. Evaluation of itch was reported on a 10 cm VAS. Zinc sulfate probably reduces uraemic itch (Analysis 3.1.3 (2 studies, 76 participants): MD -1.77 cm, 95% CI -2.88 to -0.66 on VAS; moderate certainty evidence) compared to placebo.

Adverse effects

Mapar 2015 reported vomiting in one participant in the placebo group and Najafabadi 2012 did not specify exact adverse effects, only that none were "attributable to zinc sulfate".

Oral ergocalciferol versus placebo

Shirazian 2013 compared 50,000 IU oral ergocalciferol/week and placebo. Itch was reported with the results of a 21-point customised itch questionnaire. Ergocalciferol may make little or no difference to uraemic itch (Analysis 3.1.4 (1 study, 50 participants): MD 0.40, 95% CI -2.48 to 3.28; low certainty evidence) compared to placebo.

No adverse effects were reported in the ergocalciferol group.

Oral turmeric versus placebo

Pakfetrat 2014compared 22 mg oral turmeric 3 times/day and placebo. Itch was evaluated with a 40-point modified Duo scale. Turmeric probably reduces uraemic itch (Analysis 3.1.5 (1 study, 100 participants): MD -6.40, 95% CI -7.42 to -5.38 on modified Duo scale; moderate certainty evidence) compared to placebo.

No adverse effects are reported in the intervention group.

Oral Fumaria parviflora versus placebo

Akrami 2017 compared 1 g oral Fumaria parviflora 3 times/day of with placebo. Itch was evaluated on a 10 cm VAS. Fumaria parviflora may reduce uraemic itch (Analysis 3.1.6 (1 study, 63 participants): MD -3.90 cm, 95% CI -5.04 to -2.76 on modified Duo scale; low certainty evidence) compared to placebo.

A few mild abdominal symptoms were observed in both the Fumaria parviflora and placebo groups.

4. Dialysis modality

See Summary of findings 3; adverse effects Table 4.

High flux/permeability haemodialysis versus conventional haemodialysis

Three studies (Chen 2009; Hui 2011; Jiang 2016) compared high flux/permeability HD to conventional HD. Evaluation of itch used a 10 cm VAS. High flux/permeability HD may decrease uraemic itch (Analysis 4.1.1 (3 studies, 202 participants): MD -2.62 cm, 95% CI -3.72 to -1.52; I^2 = 67%; low certainty evidence) compared to conventional HD.

These studies did not report on adverse effects.

Haemodialysis with haemoperfusion versus conventional haemodialysis

Li 2017a compared conventional HD with HD using neutral macroporous resin haemoperfusion with one of two different resin perfusers. Evaluation of itch used a 10 cm VAS. HD with haemoperfusion therapy may decrease uraemic itch (Analysis 4.1.2 (1 study, 202 participants): MD -2.37 cm, 95% CI -2.89 to -1.85; low certainty evidence) compared to conventional HD

This study did not report on adverse effects.

Haemodiafiltration with haemoperfusion against high-flux haemodialysis

Zhang 2016a compared haemodiafiltration with haemoperfusion to high-flux HD. They reported that haemodiafiltration with haemoperfusion was significantly more effective in relieving itch than high-flux HD measured on a VAS.

This study did not report on adverse effects.

High-flow versus conventional flow haemodialysis

Aliasgharpour 2018 compared high-flow HD with conventional flow HD. They reported a significant reduction in severity in itch with high-flow HD measured on a 4-point VAS.

This study did not report on adverse effects.

Haemodialysis solutions

Carmichael 1988 compared magnesium-free dialysate with conventional dialysate containing magnesium. They reported no significant itch reduction on a VAS.

Rad 2017 compared cool dialysate with conventional dialysate at a normal temperature. They reported cool dialysate was significantly more effective in relieving uraemic pruritus.

Kyriazis 2000 crossed over four patients with variable concentrations of calcium in their dialysate and reported a non-significant trend towards lower calcium concentrations reducing uraemic itch.

5. Other interventions

See Summary of findings 3; adverse effects Table 5.

UV-B radiation

Four studies (Blachley 1985; Gilchrest 1979; Ko 2011; Sherjeena 2017) compared UV-B radiation versus placebo (typically UV-A) exposure 3 times/week for the reduction of CKD-related uraemic pruritus. Due to the mechanism of the intervention there was often inherent difficulties in blinding the administrators and patients. Outcomes included both Duo score and percent of patients experiencing absolute relief.

UV-B radiation may make little or no difference to uraemic itch (Analysis 5.1.1 (4 studies, 86 participants): SMD -2.49, 95% CI -4.62 to -0.41; I^2 = 93%; low certainty evidence) compared to UV-A/placebo

UV-A radiation was not originally included in this systemic review as an intervention category. During the 1980s some RCTs (including Sanchez 1986 and Taylor 1983) investigated UV-A and found that it likely does not decrease uraemic itch. UV-A has been commonly used as a placebo in RCTs of analogous interventions.

Chan 1995 reported a significant reduction in itch in the UV-B group but did not report the results of the placebo intervention.

Common adverse effects across all studies included sunburn and tanning; these were also seen in the control UV exposures.

Thermal therapy

Hsu 2009 compared thermal (warming) therapy with a placebo patch. Evaluation of itch used a 10 cm VAS. Thermal therapy may make little or no difference to uraemic itch (Analysis 5.1.2 (1 study, 42 participants): MD -2.06 cm, 95% CI -6.54 to 2.42; low certainty evidence) compared to the placebo patch.

This study did not report on adverse effects.

DISCUSSION

Summary of main results

This systematic review assesses 92 RCTs evaluating 43 different interventions. Evidence for most interventions include only a single placebo controlled trial, often underpowered. However, the number of studies, participants, statistical power, and evidence quality significantly improves for several interventions. Less often, one intervention was compared to another allowing for some informal indirect comparisons between treatments. Fortunately, the majority of interventions include studies reporting itch with a well-validated VAS or Duo's scores aiding in the interpretation of the results. These results allowed reporting as MD or SMD with most interventions.

The results are reported in Summary of findings 1; Summary of findings 2; Summary of findings 3. The grouping of the GABA analogues, kappa opioid agonists, Mu opioid antagonists, polyunsaturated fatty acids, and UV-B radiation assumed their class effect corroborated by previous studies on their effectiveness in uraemic pruritus, non-specified pruritus, and related pathophysiology such as pain. For instance pregabalin and gabapentin, known to have similar and highly correlative downstream effects, are studied together for their classed effect on uraemic pruritus (Matsuda 2016). They have also been shown through a head-to-head RCT to have similar efficacy in treating uraemic pruritus (Solak 2012). Finally, the results of this

review's placebo-controlled gabapentin and pregabalin RCTs are homogeneous, again supporting this classification.

Five interventions included multiple and/or larger studies with a combined sample size of over 100 participants: GABA analogues, kappa opioid agonists, ondansetron, capsaicin cream, and turmeric. Each of these has no identified major sources of bias limiting their interpretation. Of the five, only ondansetron was not found to be associated with a reduction in uraemic itch versus placebo. GABA analogues achieved the largest effect size of all interventions. The effect size of kappa opioid agonists and capsaicin cream are both modest in comparison. One direct comparison (GABA analogues versus. Ondansetron) was consistent with above with similar effect size to those of the GABA analogue versus placebo RCTs. Supplementing this data on gabapentin and pregabalin are five mixed quality RCTs favouring gabapentin in direct comparison to various antihistamines.

The small sample sizes and often significant sources of bias limit the conclusions drawn from the majority of this review's other interventions. No meaningful quantitative analysis can be drawn from the adverse effects of the interventions due to insufficient and disorganised reporting. As a global assessment, adverse effects of nearly all antipruritic interventions are somewhat uncommon and non severe. One exception may be kappa opioid agonists where adverse effects were slightly more common.

While most studies provided adequate data to contribute to an analysis of itch reduction, few reported on any of the secondary outcomes (e.g. sleep, QoL) described by our protocol. Of the secondary data reported, the conclusions are limited by heterogeneous outcomes and low individual study quality.

Overall completeness and applicability of evidence

Recruited patients included only those already on HD or those with an expectation to begin shortly. All studies outlined prolonged and ongoing significant itch coinciding with CKD as inclusion criteria. Nearly every RCT also outlined exclusion criteria to exclude patients with pathology that potentially otherwise explains their itch symptoms (e.g. dermatological or liver disease). The applicability of the evidence derived from this meta-analysis may be weaker in populations who have potential non-renal causes to their itch pathology. This was notable as many patients living with CKD do not have the disease in isolation.

Given the diversity of the interventions and relatively modest number of studies per intervention, it was not possible to make comparisons on the effectiveness of all interventions. For instance, Solak 2012 found both gabapentin and pregabalin to be equally and highly efficacious in reducing uraemic itch. Missing data and inconsistent reporting did not allow us to include data from all studies in the quantitative meta-analyses. Approximately 70% of all participants (in studies that met protocol inclusion criteria) contributed to our meta-analyses and the remainder were qualitatively analysed. Patient characteristics in the quantitative and qualitative analyses are very similar.

Multiple studies noted that recruited patients had already failed one anti-itch treatment prior to being randomised. The most common previous treatment was an antihistamine despite the lack of substantial evidence for its use for uraemic itch. It is unclear if prior antihistamine treatment could be a confounding factor.

Some interventions that are yet to be studied via an RCT are currently recommended by guidelines and authorities for uraemic itch. Often, they are also routinely used in clinical practice. Without at least one placebo-controlled RCT it is beyond the scope of this systematic review to assess this evidence in a quantitative manner.

There have not been sufficient RCTs using different dosing regimens to give definitive recommendations about the doses of specific interventions. The populations included in the RCT's tend to be younger than the typical population with CKD. The elderly may be more susceptible to side effects from these drugs. In the case of GABA analogues, evidence from Noshad 2011 and Rayner 2012 suggest that a low dose of gabapentin (100 mg/day) or pregabalin (25 mg/day) should be used initially and then titrated up.

This systematic review's recommendation on individual interventions as monotherapy are generalisable to patients with CKD and chronic itching with no other obvious cause. Thus, there is strong external validity extending to this review's outlined population (patients with stage 4 and 5 CKD and established CKD-related itch).

Quality of the evidence

Certainty of the evidence varied widely. High quality evidence exists for GABA analogues, kappa opioid agonists, and ondansetron. These interventions draw conclusions from multiple independent well-powered RCTs with no significant biases identified. There was moderate quality evidence for several other inventions Summary of findings 1; Summary of findings 2; Summary of findings 3. The most common factor limiting the certainty of the evidence was the reliance on a single underpowered RCT. Many of these studies are clearly underpowered with limited participants and large standard error. Other common reasons include the use of a non-validated itch severity outcome measures, insignificant magnitude of effect, and other significant sources of bias.

Most studies had low or unclear risk of bias across the majority of domains (Figure 2 and Figure 3), however results of this review should be interpreted with caution. Increased risk of bias appears correlated with earlier dates of publication. In this review, underpowered interventions often had increased risk across most of the bias categories. This aside, there are many interventions (both of small and large sample sizes) with low overall risk of bias profiles Figure 2.

Potential biases in the review process

Several intervention are grouped (most notably GABA analogues, Kappa agonists, Mu antagonists, and antihistamines) within the quantitative and qualitative analysis. Opioids, GABA analogues, and antihistamines all have a body of literature externally supporting this "class effect". Additionally, within this systematic review, consistent effects sizes, standard error, and adverse effects provide strong internal validity to this categorisation. However, this inevitably poses a potential for bias and warrants highlighting.

Several cross-over studies within this review reported results consistent with parallel RCTs. This approach gives rise to a unit-of-analysis error with CIs that are likely to be too wide, and the study would receive too little weight, with the possible consequence of disguising clinically important heterogeneity. This was somewhat mitigated by verifying that our calculated results match those that

are partially reported and also by an overall sensitivity analysis targeting these "approximated" studies.

This review only examined RCTs. All included studies, save one, were blinded. Chilled baby, some UV-B, and some HD modality interventions are unlikely to have been able to blind their participants due to the inherent nature of the intervention. Six studies included significant statements of declaration; all declared significant financial conflicts of interest relating to the pharmaceutical manufacturers of those interventions. However, these were unlikely to bias the major findings of this review.

This systematic review addressed a clear research questions and used predefined inclusion criteria to select and appraise studies. We conducted extensive and sensitive searches but the possibility of publication bias remains. This was especially true for interventions with only one RCT identified. Our protocol did not include exhaustive exclusion criteria for patients potentially with pathology associated with non-uraemic itch. It should be noted that the majority of RCTs in this review excluded such patients.

The review did not impose language restrictions. Seven studies were translated prior to data extraction.

A comprehensive search of the literature was performed by searching multiple databases and well as handsearching for potential RCTs in the grey literature. All possible relevant data was extracted and whenever studies' reporting proved insufficient the relevant author(s) were contacted or studies were cross checked in the relevant clinical trials registry. Approximately half of all such cases recovered additional original data. Registers of ongoing trials and available conference proceedings were also searched.

Of the studies qualifying for this review, many did not, or only superficially, reported on adverse effects. Overall, the adverse effects reported were somewhat uncommon and generally mild in nature. Often no adverse effects occurred. It was possible that in some studies the authors did not bother to report the lack of adverse effects occurring, however this was not helpful for drawing accurate conclusions. Other secondary outcomes investigated were rarely reported. Significant results of either adverse effects or important secondary outcomes that go unreported may bias the results of this review.

Agreements and disagreements with other studies or reviews

This systematic review found similar results relative to other reviews on the treatment uraemic pruritus. Our search revealed three recent reviews on pathological itch in general. Two are specifically CKD-related.

Siemens 2016 examined 947 CKD participants in 36 trials. The review included all patients in the palliative care setting, did not focus on non-pharmacological interventions, and excluded trials comparing interventions. The review did not exclusively focus on patients with CKD. Additionally, substantial new evidence on GABA analogues, ondansetron, and new pharmacological interventions have been published since their search. This new evidence and our review is consistent with the overall findings of Siemens 2016, but notably provided increase power to the positive findings on GABA analogues, kappa opioid agonists, and the non-efficacy of ondansetron.

Pongcharoen 2015 examined participants in 26 trials in a quasi-systematic review of all systemic anti-itch treatments. Again, this review did not exclusively focus on patients with CKD. Less than half of all trials involved patients with CKD.

Simonsen 2017 examined participants in 44 trials examining pharmacological, alternative, and adjunctive interventions. These included interventions such as acupuncture which was not included in our review. The limited number and degree of heterogeneity of the studies did not permit formal meta-analysis. While the authors did not comment on kappa agonists and ondansetron their results on gabapentin are consistent with the findings of our review.

Other more focused reviews examined the effect of the GABA analogue gabapentin (Lau 2016), opioid receptor antagonist (Phan 2010), and topical capsaicin (Gooding 2010) on uraemic pruritus. Again, the results of this systematic review are consistent with these reviews. Of note, this is the first quantitative meta-analysis of uraemic pruritus on this scale.

AUTHORS' CONCLUSIONS

Implications for practice

A large number of interventions were examined in this review. Some treatment modalities appear to be effective in the reduction of uraemic itch, others may be of some possible effectiveness, and several appear to have minimal or no effectiveness.

Of all treatments for uraemic pruritus GABA analogues have been studies by the greatest number of RCTs and each have been shown to have the greatest effect size versus all other inventions studied. GABA analogues reduce itch in patients with CKD. Within GABA analogues most of the evidence was for gabapentin with the rest for pregabalin. Even with the removal of pregabalin trials, these results remain consistent. A further RCT, even of on the scale of the largest GABA analogue trials included in this review, is unlikely to substantially change this result.

There have not been sufficient RCTs using different dosing regimens to give definitive recommendations about dosage. Both scheduled dosing and titrating dosages frequency occur.

Evidence in this review show that Kappa opioid agonists slightly reduce itch in patients with CKD. Additionally, indirect comparisons to other interventions suggest a much more modest effect in comparison to GABA analogues. Nalfurafine is the kappa opioid agonist with the largest and highest quality body of evidence.

Ondansetron was also well studied in multiple RCTs, bur does not appear to reduce uraemic itch. This was again with high certainty of evidence.

Oral montelukast, turmeric, zinc sulfate, and topical capsaicin all probably reduce uraemic pruritus, but additional high quality evidence is required before a decisive conclusion can be made.

Guidelines do not often recommend gabapentin as first line treatment in uraemic itch. Many of the included RCTs note that it is often standard practice to prescribe antihistamines initially. Research has shown most medical directors continue to prescribe antihistamines as first line in the majority of cases (Rayner 2017). Conclusions from this systematic review may influence this policy.

This review may also be a guide for a changing role for treatment modalities where evidence was lacking. Erythropoietin, thalidomide, cromolyn, doxepin, nicergoline, cholestyramine, nicotinamide, sodium thiosulfate, and lidocaine are of questionable utility in the treatment of uraemic pruritus. Ondansetron was not efficacious. It is somewhat unlikely the further study on ondansetron will change this result. Currently, there is insufficient data for the other interventions to infer in either direction.

Implications for research

The effectiveness of GABA analogues may guide future study into the underlying mechanisms of uraemic pruritus. GABA analogues may also serve as a target for research in non-uraemic pruritus which has mostly focused on interventions with unrelated mechanisms of action. While shown to be efficacious, the optimal dosing of gabapentin and pregabalin would benefit from targeted study. Finally, several interventions investigated by this systemic review would benefit from additional appropriately powered RCTs. In particular the interventions turmeric, topical capsaicin, montelukast, high flux or permeability HD, and oral cromolyn have limited, but potentially promising preliminary trials.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Afrasiabifar 2017

Study characteristics

Methods	• Study design: parallel RCT • Time frame: recruitment date 23 August 2013; study lasted 40 days

Afrasiabifar 2017 *(Continued)*

	• Duration of study/follow-up: 2 weeks
Participants	• Setting: multicentre (3 affiliated units) • Country: Iran • Inclusion criteria: pruritus of unknown cause in patients aged > 18 years on HD for at least 6 months • Number (randomised/analysed): treatment group (22/22); control group (22/20) • Mean age ± SD (years): treatment group (58.4 ± 17.4); control group (50.8 ± 16.5) • Sex (M/F): treatment group (12/10); control group (10/10) • Comorbidities: not reported • Exclusion criteria: kidney transplant recipient; noncompliance; long-term antihistamine use; psychological/cognitive/audio-visual disorders
Interventions	Treatment group • Sweet almond oil (topical): 100 mg/day for 2 weeks Control group • No intervention
Outcomes	• Duo score: MD at each week reported with specific P values
Notes	• Conflicts of interest: not reported • Zahra Mehri, School of Nursing and Midwifery, Yasuj University of Medical Sciences (YUMS), Yasuj, IR Iran. Tel: +98-7433234115, Fax: +98-07433234115, E-mail: zahra.mehri@yums.ac.ir

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "...allocated to two groups test and control using block randomization."
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo group
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No placebo group, not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than %10 attrition per study protocol
Selective reporting (reporting bias)	Low risk	Specified results clearly reported
Other bias	Low risk	No evidence of publication, funding, or other confounding bias

Akrami 2017

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: September 2015 to December 2015 • Duration of study/follow-up: 8 weeks
Participants	• Setting: single centre (outpatients) • Country: Iran • Inclusion criteria: > 18 years, on HD with pruritus for at least 6 weeks, were sufficiently dialysed with a minimum single Kt/V of 1; not improved with conventional drugs • Number (randomised/analysed): treatment group (39/32); control group (40/31) • Mean age ± SD (years): treatment group (53.5 ± 14.2); control group (57.3 ± 13.4) • Sex (M/F): treatment group (21/11); control group (19/12) • Relevant comorbidities: not reported • Exclusion criteria: Hepatobiliary diseases; respiratory ailments; malignancy; allergic diathesis; any dermatologic diseases that induce pruritus; or receiving immunosuppressive therapy
Interventions	Treatment group • Fumaria parviflora (oral): 2 x 500 mg capsules, 3 times/day for 8 weeks Control group • Placebo (oral): 2 wheat flour capsules, 3 times/day for 8 weeks
Outcomes	• Pruritus: VAS score mean reduction • Adverse effects * QUOTE: "In the FP group, four patients experienced gastric pain that led to two patients dropping out of the study. One patient complained of small rashes on both legs and feet, but this did not lead to drug discontinuation. In the placebo group, abdominal cramps in one patient and constipation in another patient led to two patients dropping out of the study."
Notes	• Supported by Shiraz University of Medical Sciences (grant number: 94-7535) • Pouya Faridi, Department of Phytopharmaceuticals, School of Pharmacy and Pharmaceutical Sciences Research Center, Shiraz University of Medical Sciences, Shiraz, IR Iran. Tel/Fax: +98-7132337589, E-mail: pouya_faridi@yahoo.com

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	QUOTE: "Balanced blocked randomization with a block size of four was used."
Allocation concealment (selection bias)	Low risk	QUOTE: "Each set of eight bottles were packed into one container, each of which was numbered for each patient." "Code-breaking was carried out after data analysis."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "All the participants and the investigator were blinded to group assignment."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	QUOTE: "All the participants and the investigator were blinded to group assignment."

Akrami 2017 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts: treatment group (9); control group (7)
Selective reporting (reporting bias)	Low risk	Results clearly and fully reported
Other bias	Low risk	No evidence of publication, funding, or other confounding bias

Aliasgharpour 2018

Study characteristics

Methods	• Study design: parallel RCT • Time frame: 2011 • Duration of study/follow-up: 4 weeks
Participants	• Setting: single centre (outpatients) • Country: Iran • Inclusion criteria: HD 3 times/week for 4 hours for at least 6 months; pruritus (mild, moderate, and severe) • Number: treatment group (25); control group (22) • Mean age (years): treatment group (52); control group (44) • Sex (M): treatment group (68%); control group (86%) • Relevant comorbidities: not reported • Exclusion criteria: BP < 100/60 mmHg; hospitalisation due to acute problem; death; skin disease that cause pruritus; active hepatobiliary disease; severe heart disease
Interventions	Treatment group • High flow: rate of blood flow was increased in the first 2 weeks and the second 2 weeks by 25 and 50 rounds/min compared to the mean rate of blood flow of HD device in the last 2 sessions before intervention Control group • No change in dialysis
Outcomes	• Pruritus severity: 4 point scale (none, low, medium, severe)
Notes	• No declared conflicts of interest • Soheila Zabolypour, B.S., M.S., Clinical Cares and Skills Research Center, • Instructor of Nursing, Department of Medical Surgical Nursing, School of Nursing and Midwifery, Yasuj University of Medical Sciences, Yasuj, IR Iran, email: s_zabolypour@yahoo.com

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "They were divided into two groups of experimental and control as random allocation block"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

Aliasgharpour 2018 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "Single blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	QUOTE: "The interviewer did not know the patients grouping into intervention and control"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	10 dropouts post-randomisation
Selective reporting (reporting bias)	Unclear risk	Not specified what metrics of severity are being tested
Other bias	Unclear risk	During the study 72% and 52% of patients in the experimental and control group consumed medications such as antihistamines, Renagel, hydroxyzine, erythropoietin, and gabapentin No evidence of publication or funding bias

Amirkhanlou 2016

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: 2013 • Duration of study/follow-up: 2 weeks
Participants	• Setting: single centre (inpatients) • Country: Iran • Inclusion criteria: patients with uraemic pruritus undergoing HD • Number: treatment group 1 (26); treatment group 2 (26) • Mean age ± SD (years): treatment group 1 (53.5 ± 14.2); treatment group 2 (60.2 ± 7.4) • Sex (M/F): treatment group 1 (12/14); treatment group 2 (13/13) • Relevant comorbidities: not reported • Exclusion criteria: non-uraemic pruritus
Interventions	Treatment group 1 • Gabapentin (oral): 100 mg/day for 2 weeks Treatment group 2 • Ketotifen (oral): 1mg twice/day for 2 weeks

Outcomes	• Pruritis severity score: 0 to 4 point custom itch severity scale converted to response at end of study
	  * Complete response: 0-1
	  * Partial response: 2-3
	  * No response: 4
	• Adverse effects: drowsiness, dizziness

Notes	• No declared conflicts of interest • Supported by Shiraz University of Medical Sciences (grant number: 94-7535)

Amirkhanlou 2016 *(Continued)*

- Dr. Anna Rashedi, MD
- E-mail: anna_rashedi@yahoo.com

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "double-blind randomised, Patients were randomly assigned to two groups "
Allocation concealment (selection bias)	Unclear risk	QUOTE: "double-blind randomised"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "double-blind randomised, patients and drug distributors were not aware of the prescribed medications "
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	QUOTE: "double-blind randomised, patients and drug distributors were not aware of the prescribed medications"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients randomised completed the study
Selective reporting (reporting bias)	High risk	Baseline scores not reported, raw scores not reported
Other bias	Low risk	No evidence of publication, funding, or other confounding bias

Aramwit 2012a

Study characteristics

Methods	• Study design: in-subject, split-body RCT • Time frame: not reported • Duration of study/follow-up: 6 weeks
Participants	• Setting: single centre (inpatients) • Country: Thailand • Inclusion criteria: > 18 years; HD for at least 3 months; mild to severe CKD-related pruritus as measured by VAS during the previous 6 weeks • Number: 50 patients; 47 completed the study • Mean age ± SD: 49.6 ± 11.2 years • Sex M/F: 17/30 • Relevant comorbidities: not reported • Exclusion criteria: children; pruritus caused by other skin diseases or medication; patients who were allergic to any compounds in the formula; other diseases related to systemic pruritus; patients who had skin problems or rashes on their extremities
Interventions	Treatment group • Sericin (topical): 1g in 30 mL water, twice a day for 6 weeks

Aramwit 2012a *(Continued)*

	Control group • Placebo (topical): twice a day for 6 weeks
Outcomes	• Pruritus: mean VAS score every 2 weeks including baseline
Notes	• Conflicts of interest: not reported • Correspondence: aramwit@gmail.com • Bioactive Resources for Innovative Clinical Applications Research Unit and Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok 10330, Thailand

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "The physician investigator enrolled the subjects into this study, and using a computer-generated block of four, another investigator generated the random allocation sequence that divided the patients into two groups. The identities of the patients in each group were concealed from both the investigators and the patients."
Allocation concealment (selection bias)	Low risk	QUOTE: "The physician investigator enrolled the subjects into this study, and using a computer-generated block of four, another investigator generated the random allocation sequence that divided the patients into two groups. The identities of the patients in each group were concealed from both the investigators and the patients."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "The identities of the patients in each group were concealed from both the investigators and the patients"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	QUOTE: "The identities of the patients in each group were concealed from both the investigators and the patients"
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 dropouts (6%) "due to relocation". Unlikely to influence patients' body part/sides served as controls
Selective reporting (reporting bias)	Unclear risk	Split body trial with only aggregate intervention level data without patient level comparisons provided
Other bias	Low risk	No evidence of publication, funding, or other confounding bias

Ashmore 2000

Study characteristics

Methods	• Study design: cross-over RCT • Time frame: enrolment from November 1995 to October 1996 • Duration of study/follow-up: 6 weeks (2 x 1 week washout + 2 week study)
Participants	• Setting: single centre (inpatients) • Country: UK • Inclusion criteria: patients ≥ 18 years on HD with pruritus not controlled by standard treatments

Ashmore 2000 *(Continued)*

	• Number: 16 • Median age, range: 60, 28 to 77 years • Sex (M/F): 10/6 • Relevant comorbidities: not reported • Exclusion criteria: children
Interventions	Treatment group • Ondansetron (oral): 8 mg twice/day for 2 weeks Control group • Placebo (oral): twice/day for 2 weeks
Outcomes	• Pruritis: VAS score collected daily with the median and IQR reported at the baseline of each intervention and washout period
Notes	• Supported by grant from Glaxo Group Research and Yorkshire Kidney Research Fund • Correspondence: Colin H. Jones MD, Renal Unit, York District Hospital, York, UK, colin-jones@brimham.demon.co.uk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "Participants were randomised to receive active drug and placebo in a double-blind crossover study."
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "Participants were randomised to receive active drug and placebo in a double-blind crossover study."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	QUOTE: "Patients recorded the intensity of pruritus each day on a 0-to-10 visual analogue scale" Patient assessed VAS
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3/19 dropouts. Dropouts were balanced. Not ITT
Selective reporting (reporting bias)	Low risk	Cross-over study, protocol in advance, both periods combined reported
Other bias	Unclear risk	Supported by grant from Glaxo Group Research and Yorkshire Kidney Research Fund

Aubia 1980

Study characteristics

Methods	• Study design: parallel RCT • Time frame: 10 month time period

Aubia 1980 *(Continued)*

	• Duration of study/follow-up: 4 weeks
Participants	• Setting: single centre (outpatients) • Country: Spain • Inclusion criteria: HD patients with a customised pruritus score 5 and above • Number: treatment group (6); control group (7) • Mean age ± SD (years): not reported • Sex (M/F): 8/5 • Relevant comorbidities: not reported • Exclusion criteria: aged < 18 years
Interventions	Treatment group • Cimetidine (oral): 600 mg/day for 4 weeks Control group • Placebo (oral): daily for 4 weeks
Outcomes	• Pruritus: custom itch consisting of intensity, duration, and localization score totalling 0 to 8. Only P values and t scores reported
Notes	• No declared source of funding • Correspondence: Nephrology Service, Hospital Gral. M.D. Esperanca, S. Josep de la Muntanya, 12 Barcelona

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "...included in a double blind randomised study that evaluated the effects of classic antihistaminic (group AH) before the effects of a placebo (P) during 4 weeks."
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "...included in a double blind randomised study that evaluated the effects of classic antihistaminic (group AH) before the effects of a placebo (P) during 4 weeks."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts post randomisation
Selective reporting (reporting bias)	High risk	Only P-values and t-scores reported; unable to meta-analyse
Other bias	Low risk	No evidence of publication or funding bias

Baumelou 1993

Study characteristics	
Methods	• Study design: cross-over RCT • Time frame: 8 weeks • Duration of study/follow-up: 8 weeks
Participants	• Setting: multicentre • Country: France • Inclusion criteria: HD patients • Number (randomised/analysed): 50/30 • Mean age ± SD (years): not reported • Sex (M/F): not reported • Relevant comorbidities: not reported
Interventions	Treatment group 1 • Cetirizine (oral): 10 mg once/day Treatment group 2 • Dexchlorpheniramine (oral): 6 mg once/day Control group • Placebo
Outcomes	• Cumulative decrease in VAS and 4-point efficacy scale • Side effects
Notes	• Abstract-only publication • Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	QUOTE "determined by randomization"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE "double blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	QUOTE "double blind"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	11 dropouts
Selective reporting (reporting bias)	High risk	Only percentage change and P-values reported

Baumelou 1993 *(Continued)*

Other bias	Unclear risk	Abstract-only publication

Begum 2004

Study characteristics

Methods	• Study design: parallel RCT • Time frame: 2004 • Duration of study/follow-up: 16 weeks
Participants	• Setting: multicentre (3 sites) (inpatients) • Country: USA • Inclusion criteria: HD patients aged > 20 years with pruritis • Number: treatment group 1 (12); treatment group 2 (10) • Mean age ± SD (years): treatment group 1 (60.2 ± 19.4); treatment group 2 (49.2 ± 18.1) • Sex (M/F): treatment group 1 (6/6); treatment group 2 (7/3) • Relevant comorbidities: not reported • Exclusion criteria: DM; malabsorption problems; conditions that may affect fatty acid metabolism
Interventions	Treatment group 1 • Fish oil (oral): 6 g ethyl ester/day for 16 weeks Treatment group 2 • Safflower oil (oral): 6 g ethyl ester/day for 16 weeks
Outcomes	• Pruritus: Duo score • Adverse effects
Notes	• No declared conflicts of interest • Louise Peck, PhD, RD, Department of Epidemiology, University of Washington, PO Box 353410, Seattle, WA 98195. E-mail: lpeck@u.washington.edu

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "randomised"
Allocation concealment (selection bias)	Unclear risk	QUOTE: "randomised"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "packaged in similar soft gel capsules containing 1 g ethyl ester each"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	QUOTE: "packaged in similar soft gel capsules containing 1 g ethyl ester each"
Incomplete outcome data (attrition bias)	Low risk	No dropouts and complete reporting

Begum 2004 *(Continued)*

All outcomes

Selective reporting (reporting bias)	Low risk	No dropouts and complete reporting
Other bias	Low risk	No evidence of publication or funding bias

Bhaduri 2006

Study characteristics

Methods	• Study design: crossover RCT • Time frame: 5 weeks • Duration of study/follow-up: 5 weeks
Participants	• Setting: multicentre (number of sites not reported) • Country: Japan • Inclusion criteria: patients with pruritus aged 40 to 80 years receiving HD treatment 3 times/week for ≥ 3 months • Number: treatment group 1 (26); treatment group 2 (27); control group (25) • Mean age ± SD: not reported • Sex M/F: not reported • Relevant comorbidities: not reported • Exclusion criteria: not reported
Interventions	Treatment group 1 • Nalfurafine: 5 µg infusion post dialysis Treatment group 2 • Nalfurafine: 2.5 µg infusion post dialysis Control group • Placebo
Outcomes	• Cumulative decrease in VAS
Notes	• Abstract-only publication • Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE "randomised"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Insufficient information to permit judgement

Bhaduri 2006 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Baseline, percent change and CI reported
Other bias	Unclear risk	Abstract-only publication

Blachley 1985

Study characteristics

Methods	• Study design: parallel RCT • Time frame: • Duration of study/follow-up: 2 weeks
Participants	• Setting: single centre (outpatients) • Country: USA • Inclusion criteria: chronic HD with VAS ≥ 7 • Number: treatment group (9); control group (8) • Mean age ± SD: 49.6 ± 11.2 years • Sex M/F: 17/30 • Relevant comorbidities: not reported • Exclusion criteria: children; other dermatological comorbidities
Interventions	Treatment group • UVB (total body exposure): 0.19 nJ/cm^2/sec 3 times/week for 2 weeks Control group • UVA (total body exposure): 3 times/week for 2 weeks
Outcomes	• Pruritus: mean VAS score at baseline and 2 weeks; mean changes and SDs obtained from charts and text
Notes	• Supported by the United States Veterans Administration. • Correspondence: Correspondence: Jon D. Blachley. MD (151). Dallas • U4MC. 4500 S Lancaster Rd. Dallas. TX 75216

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "17 pruritic hemodialysis patients were randomised to one of two treatment groups: UVA (placebo) or UVB phototherapy."

Blachley 1985 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	QUOTE: "In a single blinded fashion"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Patient reported VAS scores
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No post randomisation dropouts
Selective reporting (reporting bias)	Unclear risk	No placebo results explicitly reported. Reported in bar graph
Other bias	Low risk	QUOTE: "Supported by the United States Veterans Administration." No evidence of publication, funding, or other confounding bias

Boaz 2009

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: not reported • Duration of follow-up: 2 weeks
Participants	• Setting: single centre (outpatients) • Country: Israel • Inclusion criteria: patients with pruritus aged 40 to 80 years receiving HD treatment 3 times/week for ≥ 3 months • Number: treatment group (25); control group 1 (25); control group 2 (28) • Mean age ± SD: 67.8 ± 12.9 years • Sex M/F: 57/43 • Relevant comorbidities: patients of both genders, without regard to comorbidities or prescribed medications, were eligible • Exclusion criteria: not reported
Interventions	Treatment group (DS) • Dead sea lotion group (topical): entire body lotion, twice/day for 2 weeks Control group 1 (P1) • Identical to the active treatment but without Dead Sea minerals and sea silt (topical): entire body lotion, twice/day for 2 weeks Control group 2 (P2) • Identical to P1 but contained no moisturizing ingredients (Aloe barbadensis leaf juice or sodium lactate) (topical): entire body lotion, twice/day for 2 weeks

Boaz 2009 *(Continued)*

Outcomes	• 5-point Likert scale for itch • Adverse events • Absolute change and P-values reported for all comparisons
Notes	• Supported by grant from Glaxo Group Research and Yorkshire Kidney Research Fund • Correspondence: Dr. Mona Boaz, Epidemiology and Research Unit, E. Wolfson Medical Center Holon 58100 (Israel) Tel./Fax +972 3 502 8384, E-Mail mboaz8@yahoo.com

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "Randomization was conducted using an online randomiser (http://www.randomization.com) following stratification for gender and age (in 5-year categories)"
Allocation concealment (selection bias)	Low risk	QUOTE: "All were packaged in containers void of labelling except for the treatment code number and were identical in terms of shape, size and colour so that identification of treatment assignment was unknowable to the participant, study investigators and medical personnel. The code for treatment identification was held by a company representative and revealed only after data were analysed." -Treatments were unlabeled. coded, and held by a third party
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "DS, P1 and P2 were identical in colour, texture and scent. All were packaged in containers void of labelling except for the treatment code number and were identical in terms of shape, size and colour so that identification of treatment assignment was unknowable to the participant, study investigators and medical personnel. The code for treatment identification was held by a company representative and revealed only after data were analysed." -Treatments were virtually identical unlabeled. coded, and held by a third party
Blinding of outcome assessment (detection bias) All outcomes	Low risk	QUOTE: "DS, P1 and P2 were identical in colour, texture and scent. All were packaged in containers void of labelling except for the treatment code number and were identical in terms of shape, size and colour so that identification of treatment assignment was unknowable to the participant, study investigators and medical personnel. The code for treatment identification was held by a company representative and revealed only after data were analysed." -Treatments were virtually identical unlabeled. coded, and held by a third party
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	4,5,4 dropouts from DS, P1, P2
Selective reporting (reporting bias)	Low risk	Baseline and post interventions results fully reported
Other bias	High risk	Ahava Dead Sea Laboratories, Ein Bokek, Israel, provided a research grant to the research fund of the Institute of Nephrology and the Epidemiology and Research Unit at E. Wolfson Medical Center, Holon, Israel. Two of the co-authors, Miriam Oron and Zeevi Maor, are employees at Ahava Dead Sea Laboratories

Breneman 1992

Study characteristics

Methods	• Study design: parallel RCT

Breneman 1992 *(Continued)*

	• Time frame: 1992 • Duration of study/follow-up: 6 weeks
Participants	• Setting: single centre (inpatients) • Country: USA • Inclusion criteria: undergoing HD for at least 1 month and had been experiencing moderate to severe pruritus not attributable to other definable cutaneous or medical conditions • Number: 21 (number per group not reported) • Age range: 22 to 77 years • Sex (M/F): 12/9 • Relevant comorbidities: not reported • Exclusion criteria: not reported
Interventions	Treatment group • Capsaicin cream (topical): 0.025% cream, 4 times/day for 16 weeks Control group • Placebo cream (topical): daily for 16 weeks
Outcomes	• Pruritus: Duo score • Adverse effects
Notes	• Conflicts of interest: not declared • Debra L. Breneman, MD, University of Cincinnati, Department of Dermatology, 234 Goodman St., Cincinnati, OH 45267-0523

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "randomised"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	High risk	Multiple patient dropouts
Selective reporting (reporting bias)	High risk	No statistics reported
Other bias	Low risk	No evidence for publication or funding bias

Carmichael 1988

Study characteristics	
Methods	• Study design: cross-over RCT • Time frame: not reported • Duration of study/follow-up: 2 + 2 weeks
Participants	• Setting: single centre (outpatients) • Country: UK • Inclusion criteria: HD patients severely affected by uraemic itch • Number: 17 • Age range: 25 to 69 years • Sex (M/F): 16/1 • Relevant comorbidities: not reported • Exclusion criteria: not reported
Interventions	Treatment group • Magnesium-free HD for 2 weeks then swapped to control treatment Control group • Standard HD fluid with 0.85 mmol/L magnesium concentration for 2 weeks then swapped to treatment group
Outcomes	• Itch: VAS • Adverse events
Notes	• Conflicts of interest: not declared • Dr A J Carmichael, The Skin Hospital, Edgbaston, Birmingham B 15 1 PR.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: '"randomly allocated"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	QUOTE: "double blinded"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	QUOTE: "double blinded"
Incomplete outcome data (attrition bias) All outcomes	High risk	15% dropout rate, unclear allocation
Selective reporting (reporting bias)	High risk	Only "p > 0.1" reported

Carmichael 1988 *(Continued)*

Other bias	Unclear risk	No washout period. No evidence of publication or funding bias

Chan 1995

Study characteristics

Methods	• Study design: parallel RCT • Time frame: not reported • Duration of study/follow-up: 6 weeks
Participants	• Setting: single centre (outpatients) • Country: Hong Kong • Inclusion criteria: patients on dialysis with pruritic symptoms for at least 2 months and severe enough to disturb sleep or daily activities and unresponsive to oral anti-histamines and topical treatment • Number: treatment group (10); control group (9) • Mean age ± SD (years): treatment group (51 ± 2.58); control group (54 ± 4.48) • Sex M/F: not reported • Relevant comorbidities: not reported • Exclusion criteria: children; pre-existing dermatological diseases; obstructive liver disease; uncontrolled hypercalcaemia; history of SLE; photo-sensitivity that precluded phototherapy
Interventions	Treatment group • UVB: minimal erythema dose with total body exposure with coverage of face and genitalia twice/week for 6 weeks Control group • UVA: minimal erythema dose with total body exposure with coverage of face and genitalia twice/week for 6 weeks
Outcomes	• Pruritus: distribution of VAS reported as bimodal / nonlinear so means and SEs are not reported. Instead a binary response rate was defined. A P-value from a Fischer's exact test is reported
Notes	• Abstract-only publication • No declared source of funding • Correspondence: Dr. CM Chan • 813 Medical Centre, 16/F, Central Building, 1-3 Pedder • Street, Central, Hong Kong

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "...were randomised for a six-week UVB(N=10) double-blind non-crossover study against placebo (UVA, N=9)"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "double-blind non-crossover..."

Chan 1995 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	QUOTE: "Assessment was made by a single investigator who was blind-folded for the type of UV therapy to avoid observer variation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	One post-randomisation patient in the UVB group died of a stroke
Selective reporting (reporting bias)	High risk	Distribution of VAS reported as bimodal and nonlinear. No means were reported. Only P-values (Fisher exact test) and graphs
Other bias	Unclear risk	Abstract-only publication; insufficient information to permit judgement

Chen 2006e

Study characteristics

Methods	• Study design: cross-over RCT • Time frame: not reported • Duration of study/follow-up: 6 weeks; 2-week washout and 2 x 2-week treatment periods
Participants	• Setting: single centre (outpatients) • Country: Taiwan • Inclusion criteria: patients with severe refractory pruritus, on HD (Kt/V > 1.5) • Number: treatment first group (8); control first group (9) • Mean age ± SD (years): treatment first group (55.1 ± 11.5); control first group (58.2 ± 18.1) • Sex (M/F): treatment first group (3/5); control first group (5/4) • Relevant comorbidities: not reported • Exclusion criteria: causes of pruritus other than kidney failure
Interventions	Treatment group • Gamma-linolenic acid (topical): 2.2% cream 30 mL/day for 2 weeks Control group • Placebo (topical): cream 3 times/day for 2 weeks
Outcomes	• Pruritus: median and IQR VAS before and after each treatment and washout period
Notes	• No declared source of funding • Correspondence: Mai-Szu Wu, MD, Division of Nephrology, Chang Gung Memorial Hospital, 222, Mai-Chin Rd, Keelung, Taiwan. E-mail: maxwu1@adm.cgmh.org.tw

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "At the end of the baseline day, patients were randomly assigned to group A or group B."
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

Chen 2006e *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "patients applied topical GLA-rich cream or placebo cream in a double-blind fashion to their entire body"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Patient recorded pruritus score, double blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 dropout (allergic reaction to GLA cream)
Selective reporting (reporting bias)	Unclear risk	Median and IQR clearly reported for each treatment phase. Group level data without individual patient level comparisons provided
Other bias	Low risk	No evidence of publication, funding, or other confounding bias

Chen 2009

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: March 2002 to August 2007 • Duration of study/follow-up: 12 weeks
Participants	• Setting: single centre (outpatients) • Country: China • Inclusion criteria: patients on HD with uraemic pruritus unresponsive to non-dialysis treatments such as moisturising creams • Number: treatment group (58); control group (58) • Mean age ± SD (years): treatment group (43 ± 8.5); control group (42 ± 7.3) • Sex (M/F): treatment group (28/30); control group (32/26) • Relevant comorbidities: not reported • Exclusion criteria: primary diseases that may directly lead to cutaneous pruritus, including diabetic kidney disease; iPTH > 300 pg/mL
Interventions	Treatment group • High-permeability HD (F60; Fresenius) with polysulphone membranes of 1.3 m^2 and an ultrafiltrate coefficient of 40 mL/h/mmHg; 3 times/week for 12 weeks Control group • Conventional dialysers (F6; Fresenius) were used, with polysulphone membranes of 1.3 m^2 and an ultrafiltrate coefficient of 5.5 mL/h/mmHg; 3 times/week for 12 weeks
Outcomes	• Reduction in itch on VAS
Notes	• No declared conflicts of interest • Dr Wan Xin Tang, Department of Nephrology, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, People's Republic of China. E-mail: jjbb77777@163.com
Risk of bias	

Chen 2009 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "An independent technician allocated the patients into one of two groups, either HPHD or CHD, according to a random-number table"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "double blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	QUOTE: "double blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts after randomisation
Selective reporting (reporting bias)	Low risk	All results clearly and fully reported
Other bias	Low risk	No evidence of publication, funding, or other confounding bias

Cho 1997

Study characteristics	
Methods	• Study design: cross-over RCT • Time frame: not reported • Duration of study/follow-up: 12 weeks (2-week baseline included, and 2-week washout in between
Participants	• Setting: single centre (inpatients) • Country: Taiwan • Inclusion criteria: patients with moderate to severe pruritus on HD (Kt/V > 1.0) • Number: treatment group (12); control group (10) • Mean age ± SD: 62 ± 4 years • Sex M/F: 14/8 • Relevant comorbidities: not reported • Exclusion criteria: dermatitis; obstructive biliary disease; DM, or malignancy
Interventions	Treatment group • Capsaicin cream (topical): 0.025%, 4 times/day for 4 weeks Control group • Placebo cream: 4 times/day for 4 weeks
Outcomes	• 4-point pruritus severity scale
Notes	• No declared source of funding • Correspondence: Der-Cherng Tarng, MD, Division of Nephrology,

Cho 1997 *(Continued)*

- Veterans General Hospital-Taipei, No 201, Sec 2 Shih-Pai Road, Taipei. 11217, Taiwan

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "Treatment order was arranged from computer generated numbers"
Allocation concealment (selection bias)	Low risk	QUOTE: "by a coauthor who did not participate in observations"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "Double blinded" and "were unknown by the observers and patients"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double blind, patients made self-evaluations, base creams ""were unknown by the observers and patients"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled patients completed the trial and were analysed.
Selective reporting (reporting bias)	Low risk	Baseline and post interventions results fully reported Intervention level data report with patient level graphical comparison comparisons provided. Correlation may inflate standard error. Carry-over effects unlikely due to washout periods.
Other bias	Low risk	No evidence of publication, funding, or other confounding bias

De Marchi 1992

Study characteristics

Methods	• Study design: cross-over RCT • Time frame: not reported • Duration of study/follow-up: 10 weeks (5 weeks each order with no washout)
Participants	• Setting: single centre (inpatients) • Country: Italy • Inclusion criteria: HD patients with minimum duration of pruritus one year • Number: 10 • Mean age ± SD: 54 ± 9 years • Sex (M/F): 6/4 • Relevant comorbidities: not reported • Exclusion criteria: history of pruritus or dermatologic disease preceding kidney failure; no comorbid dermatologics disease; systemic disease such as DM or SLE
Interventions	Treatment group • EPO (IV): 36 U/kg if HCT < 0.3, 18 U/kg otherwise; 3 times/week for 5 weeks Control group

De Marchi 1992 *(Continued)*

	• Placebo (IV): 3 times/week for 5 weeks
Outcomes	• Itch: mean Duo score collected daily reported at baseline and weekly
Notes	• No declared source of funding • Correspondence: Dr. De Marchi • Via Tartagna. 39, 33100 Udine, Italy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "patients were randomly assigned"
Allocation concealment (selection bias)	Low risk	QUOTE: "All placebo and intervention labelling hidden by treatment code." "Code broken only after completion"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "All treatment was hidden by treatment code. Both placebo and intervention delivered in the same way."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessment performed by a "single investigator who was unaware of treatment assignments" "treatment code was only broken after the trial had ended"
Incomplete outcome data (attrition bias) All outcomes	Low risk	One withdrawal in second crossover period (recorded as non-responding for at least the first week). Unclear if ITT, but unlikely to significantly influence results
Selective reporting (reporting bias)	High risk	All entered patients completed the trial and were analysed VAS documented directly from patient diaries Intervention level data without patient level comparisons provided No washout period specified
Other bias	Low risk	No evidence of publication, funding, or other confounding bias

Duque 2005

Study characteristics

Methods	• Study design: parallel RCT • Time frame: not reported • Duration of study/follow-up: 6 weeks
Participants	• Setting: multicentre (2 sites) (inpatients) • Country: USA • Inclusion criteria: patients on HD with severe itch that was resistant to conventional therapies who had at least 10 episodes of itch during a period of 2 weeks • Number: treatment group (12); control group (8) • Mean age ± SD: 59 ± 13.2 years (no data for groups reported)

Duque 2005 *(Continued)*

	• Sex: not reported • Relevant comorbidities: not reported • Exclusion criteria: children; allergy to macrolides; history of skin diseases like atopic dermatitis; other systemic diseases that could be the cause of pruritus, pruritus predating their documented kidney failure
Interventions	Treatment group • Tacrolimus ointment: 0.1% ointment (120 g tube/patient over whole study) twice/day for 4 weeks Control group • Placebo: twice/day for 4 weeks
Outcomes	• Pruritus: patient recorded VAS at baseline, week 4 and 6; 4 point scale by doctor
Notes	• Supported by Fujisawa Health Care Inc, Deerfield, Ill. • Disclosure: Dr Fleischer (coauthor) is on the Speaker's Bureau of Fujisawa, and Drs Yosipovitch and Fleischer have other research projects that are funded by Fujisawa. • Correspondence: Gil Yosipovitch, MD, Department of Dermatology, Wake Forest University School of Medicine, Medical Center Blvd, Winston Salem, NC 27157. E-mail: gyosipov@ wfubmc.edu.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "randomised, double-blind, vehicle controlled study"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "randomised, double-blind, vehicle controlled study"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Patient recorded VAS
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2 dropout in vehicle (kidney transplantation and lack of improvement) Unclear if ITT
Selective reporting (reporting bias)	High risk	No SDs reported
Other bias	High risk	Supported by Fujisawa Health Care Inc, Deerfield, Ill.

Durant-Finn 2008

Study characteristics

Methods	• Study design: parallel RCT • Time frame: December 2002 to March 2003

Durant-Finn 2008 *(Continued)*

	• Duration of study/follow-up: 12 weeks
Participants	• Setting: single centre (inpatients) • Country: Germany • Inclusion criteria: aged 29 to 82 years on dialysis with pruritis • Number: treatment group (12); control group (12) • Mean age ± SD: 53 ± 11.4 years (no data for groups reported) • Sex (M/F): 13/11 (no data for groups reported) • Relevant comorbidities: not reported • Exclusion criteria: children; pre-existing skin condition; DM
Interventions	Treatment group • L-arginine salve (topical): 25 µg/2.5 cm^2 twice/day for 6 weeks Control group • Placebo (topical): twice/day for 6 weeks
Outcomes	• Pruritus: patient recorded mean 3-point scale reported at baseline and week 2, 4, and 6
Notes	• Translated from German

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Unclear of specific method in translation, but a randomisation technique is likely used
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All 24 patients reported on for each 2-week period
Selective reporting (reporting bias)	Low risk	Main outcomes fully reported
Other bias	Low risk	No evidence of publication, funding, or other confounding bias

Fallahzadeh 2015

Study characteristics

Methods	• Study design: parallel RCT

Fallahzadeh 2015 *(Continued)*

- Time frame: not reported
- Duration of study/follow-up: 8 weeks

Participants	• Setting: single centre (inpatients) • Country: Iran • Inclusion criteria: HD patients with moderate to severe pruritus (VAS ≥ 4) of at least 6 week duration • Number: 60 "randomised into 2 equal groups" • Mean age ± SD (years): not reported • Sex (M/F): not reported • Relevant comorbidities: not reported • Exclusion criteria: secondary causes of pruritus
Interventions	Treatment group • Senna tablets (oral): given for 8 weeks; dose and frequency not reported Control group • Placebo tablets (oral): given for 8 weeks; frequency not reported
Outcomes	• Severity of itch: VAS
Notes	• Conflicts of interest not reported • No contact information given • Abstract-only publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study described as "randomised double-blind placebo-controlled"; method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	QUOTE: "double-blind"; insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	QUOTE: "double-blind"; insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Abstract-only publication; insufficient information to permit judgement

Feily 2012

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: January 2010 to July 2010 • Duration of study/follow-up: 4 weeks
Participants	• Setting: single centre (outpatients) • Country: Iran • Inclusion criteria: patients treated with HD; aged between 18 and 60 years; at least 6 weeks history of pruritus; no systemic or topical treatment for the pruritus • Number: treatment group (30); control group (30) • Mean age ± SD: 53 ± 11.4 years (data for groups not reported) • Sex (M/F): 38/22 (data for groups not reported) • Relevant comorbidities: not reported • Exclusion criteria: pregnant and breast feeding women; hypersensitivity to cromolyn sodium; any other condition except for ESKD causing pruritus; any serious systemic diseases; usage of antihistamines or other anti-pruritus drugs in the last 3 months
Interventions	Treatment group • Cromolyn sodium cream (topical): 4%, whole body coverage; twice/day for 4 weeks Control group • Placebo cream (topical): twice/day for 4 weeks
Outcomes	• Pruritus: patient recorded mean VAS (0 to 5 cm) at baseline and then weekly (5 times total)
Notes	• No declared conflicts of interest • Correspondence: Amir Feily, MD Department of Dermatology, Jondishapur University of Medical Sciences, Ahvaz, Iran Dr.feily@yahoo.com

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "Randomization was performed by using a simple random table,"
Allocation concealment (selection bias)	Low risk	QUOTE: "The placebo was formulated by a pharmacist to have a similar base with the drug but not containing the active ingredient and stored in a tube without any labelling. A similar tube was used to store CS 4% to make both creams to look physically identical."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "The placebo was formulated by a pharmacist to have a similar base with the drug but not containing the active ingredient and stored in a tube without any labelling. A similar tube was used to store CS 4% to make both creams to look physically identical."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The medications used were not revealed to their physicians
Incomplete outcome data (attrition bias) All outcomes	Low risk	All entered patients completed the trial and were analysed

Feily 2012 *(Continued)*

Selective reporting (reporting bias)	Low risk	Baseline and results clearly reported
Other bias	Low risk	No evidence of publication, funding, or other confounding bias

Foroutan 2017

Study characteristics

Methods	• Study design: parallel RCT • Time frame: not reported • Duration of study/follow-up: 4 weeks
Participants	• Setting: multicentre (6 sites) (inpatients) • Country: Iran • Inclusion criteria: HD patients aged 16 to 80 years suffering from pruritus • Number (randomised/analysed): treatment group 1 (46/37); treatment group 2 (44/35) • Mean age ± SD (years): treatment group 1 (58.8 ± 17.2); treatment group (60.6 ± 14.5) • Sex (M/F): treatment group 1 (19/18); treatment group 2 (18/17) • Relevant comorbidities: not reported • Exclusion criteria: hepatic failure; hyperthyroidism; narrow angle glaucoma; heart block; decompensated heart failure; hypotension (defined as SBP < 90 mmHg); history of allergy to pregabalin or doxepin; uncontrolled psychiatric diseases; myocardial infarction in the past 3 months; epilepsy, or even one episode of seizure; pregnancy, psoriasis, atopic dermatitis or any other condition that can justify the pruritus
Interventions	Treatment group 1 • Pregabalin (oral): 50 mg every other night for 4 weeks • In the cases of insufficient response defined as < 2 units decrease in score of VAS after one week of the therapy the dose was increased to 50 mg/day Treatment group 2 • Doxepin (oral): 10 mg every night for 4 weeks • In the cases of insufficient response defined as < 2 units decrease in score of VAS after one week of the therapy the dose was increased to 10 mg twice/day
Outcomes	• Severity of pruritis: VAS, 5-D itch scale at baseline and after 1, 2 and 4 weeks of the treatment • Dermatology life quality index (DLQI) at baseline and after 1, 2 and 4 weeks of the treatment
Notes	• No declared conflicts of interest • N. Nikvarz, Faculty of Pharmacy and Pharmaceutical Sciences, Haft-bagh Boulevard, Kerman, Iran. E-mail: nnikvarz@kmu.ac.ir

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "randomly assigned to pregabalin or doxepin based on block randomization"

Foroutan 2017 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	QUOTE: "Patients were not blind to their treatment, but who evaluated the participants and who statistically analyzed the results did not know the allocated medication of each patient"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	QUOTE: "Patients were not blind to their treatment, but who evaluated the participants and who statistically analyzed the results did not know the allocated medication of each patient"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	QUOTE: "Patients were not blind to their treatment, but who evaluated the participants and who statistically analyzed the results did not know the allocated medication of each patient"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not ITT, 9 dropouts in each arm all with justifications
Selective reporting (reporting bias)	Low risk	Clear reporting of scores at all time points
Other bias	Low risk	No evidence of publication or funding bias

Ghanei 2012

Study characteristics	
Methods	• Study design: cross-over RCT • Time frame: May to September 2008 • Duration of study/follow-up: 20 days + 14 days washout + 20 days
Participants	• Setting: multicentre (4 sites) • Country: Iran • Health status: HD patients with a minimum duration of pruritus for 3 months • Number: treatment group (11); control group (11) • Mean age ± SD (years): treatment group (59.9 ± 15); control group (53.1 ± 13) • Sex M/F: treatment group (8/3); control group (6/5) • Relevant comorbidities: not reported • Exclusion criteria: history of pruritus because of skin diseases before beginning of the kidney failure; systemic disease; anaemia (Hb < 10 g/dL), Kt/V < 1.2; on warfarin; allergy to fish oil
Interventions	Treatment group • Omega 3 fatty acid (oral): 1 g, 3 times/day for 20 days Control group • Placebo (oral): 3 times/day for 20 days
Outcomes	• Pruritus: 5-point scale twice daily. Mean percent reduction from baseline reported for washout and end of treatment periods
Notes	• No conflicts of interest declared • Correspondence: Esmat Ghanei, MD, NRC, No.103, Boostan 9th St., Pasdaran Ave., Tehran, I.R. Iran. Tel: +98 21 22567222; Email: dr_e_ghanei@yahoo.com

Ghanei 2012 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	QUOTE: "Patients were divided into two groups randomly by alternation method"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "Double blinded", "Fish oil and placebo capsules with the same shape and volume"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcomes came from "observation and interview", "double blinded" No other specific information
Incomplete outcome data (attrition bias) All outcomes	Low risk	All entered patients completed the trial and were analysed
Selective reporting (reporting bias)	Unclear risk	Results reported as percent reduction of a customised itch score Correlation may inflate standard error. Carry-over effects unlikely due to washout periods.
Other bias	Low risk	No evidence for publication, funding, or other confounding bias

Ghorbani 2012a

Study characteristics

Methods	• Study design: parallel RCT • Time frame: January to April 2010 • Duration of study/follow-up: 8 weeks
Participants	• Setting: single centre • Country: Iran • Health status: patients on dialysis; aged 18 to 60 years of age; minimum duration of pruritus 6 weeks • Number: treatment group (30); control group (30) • Mean age ± SD (years): not reported • Sex: not reported • Relevant comorbidities: not reported • Exclusion criteria: Pregnancy and breast-feeding; hypersensitivity to pimecrolimus; any other condition except for ESKD causing pruritus; and use of antihistamines or other anti-pruritus drugs in the previous 3 months
Interventions	Treatment group • Pimecrolimus ointment (topical): 1% (amount not stated), twice/day for 8 weeks Control group

Ghorbani 2012a *(Continued)*

	• Placebo (topical): twice/day for 8 weeks
Outcomes	• Pruritis: patients recorded VAS daily; mean VAS reported at baseline and 8 weeks
Notes	• Supported by a grant from Islamic Azad University of Gachsaran, Gachsaran Branch, Iran • No declared conflict of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "Randomization was performed by using a simple random table."
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "Double Blind", Patients given unlabelled medication as start of trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Patient recorded VAS
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled patients completed the trial and were analysed
Selective reporting (reporting bias)	Low risk	Baseline and results clearly reported
Other bias	Low risk	No evidence of publication, funding, or other confounding bias

Ghorbani Birgani 2011

Study characteristics

Methods	• Study design: parallel RCT • Time frame: 2010 • Duration of study/follow-up: 8 weeks
Participants	• Setting: single centre (inpatients) • Country: Iran • Inclusion criteria: patients aged 18 to 60 years with ESKD on HD • Number: treatment group 1 (30); treatment group 2 (30) • Mean age ± SD: 56 ± 13.2 years • Sex (M/F): (31/29) • Relevant comorbidities: not reported • Exclusion criteria: Skin, liver, and metabolic or any illness or condition other than kidney disease
Interventions	Treatment group 1 • Cromolyn cream (topical): 4%, twice/day for 16 weeks

Ghorbani Birgani 2011 *(Continued)*

	Treatment group 2 • Pimecrolimus cream (topical): 2%, twice/day for 8 weeks
Outcomes	• Pruritis score (VAS)
Notes	• In Arabic

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "randomised"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	QUOTE: "Blinded"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	QUOTE: "Blinded"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if any patient dropped out
Selective reporting (reporting bias)	Low risk	Full results clearly reported
Other bias	Low risk	No evidence of publication or funding bias

Gilchrest 1977

Study characteristics

Methods	• Study design: parallel RCT • Time frame: not reported • Duration of study/follow-up: 4 weeks
Participants	• Setting: single centre (inpatients) • Country: USA • Inclusion criteria: ESKD on dialysis; severe persistent pruritus • Number: treatment group (10); control group (8) • Age range: treatment group (22 to 66 years); control group (22 to 67 years) • Sex (M/F): treatment group (8/2): control group (3/5) • Relevant comorbidities: not reported • Exclusion criteria: not reported
Interventions	Treatment group

Gilchrest 1977 *(Continued)*

	• UV-B: 4.4 watts/m^2 (400 to 4800 J/m^2), twice/week for 4 weeks • Administration: 72 Westinghouse FS20T12 bulbs in parallel array Control group • UV-A: 100 watts/m^2 (1000 to 10,000 J/m^2) (dose difference to ensure that exposure was time matched and thus blinded); twice/week for 4 weeks • Administration: 4 GTE Sylvania FR74 Tl 2/PUVA Lifeline bulbs
Outcomes	• Decrease in pruritus to mild or absent (binary). Criteria for this is unclear
Notes	• Conflicts of interest not reported • Correspondence: Barbara A. Gilchrest, M.D., Department of Dermatology, Beth Israel Hospital, 330 Brookline Avenue, Boston, MA 02215

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "were randomly assigned to one of two treatment schedules"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported, similar control treatment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported, likely known to assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	6 dropouts due to unspecified concurrent illness. Unknown which arm they were randomised to. Not Intention to treat
Selective reporting (reporting bias)	High risk	Unclear grading of pruritis and not classified by patient; unable to meta-analyse
Other bias	Unclear risk	Poor/minimal exclusion criteria; no evidence of publication or funding bias

Gilchrest 1979

Study characteristics

Methods	• Study design: parallel RCT • Time frame: not reported • Duration of study/follow-up: 4 weeks
Participants	• Setting: single centre (inpatients) • Country: USA • Inclusion criteria: ESKD on dialysis; minimum duration of pruritus 2 months severe enough to disturb sleep and daily activities

Gilchrest 1979 *(Continued)*

- Number: treatment group (10); control group (8)
- Age range: treatment group (22 to 66 years); control group (22 to 67 years)
- Sex (M/F): treatment group (8/2): control group (3/5)
- Relevant comorbidities: not reported
- Exclusion criteria: children; no dermatological disease

Interventions	Treatment group • UV-B: 4.4 watts/m^2 (400 to 4800 J/m^2), twice/week for 4 weeks • Administration: 72 Westinghouse FS20T12 bulbs in parallel array Control group • UV-A: 100 watts/m^2 (1000 to 10,000 J/m^2) (dose difference to ensure that exposure was time matched and thus blinded); twice/week for 4 weeks • Administration: 4 GTE Sylvania FR74 Tl 2/PUVA Lifeline bulbs
Outcomes	• Decrease in pruritus to mild or absent (binary); criteria for this is unclear • "Nine of the 10 patients treated with UVB reported a decrease in their pruritus from severe to mild or absent, while only two of eight in the control group"
Notes	• Not reported conflicts of interest • Correspondence: Barbara A. Gilchrest, M.D., Department of Dermatology, Beth Israel Hospital, 330 Brookline Avenue, Boston, MA 02215

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "were randomly assigned to one of two treatment schedules"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported, similar control treatment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported, likely known to assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	6 dropouts due to unspecified concurrent illness. Unknown which arm they were randomised to. Not Intention to treat
Selective reporting (reporting bias)	Unclear risk	Unclear grading of pruritis and not classified by patient
Other bias	Unclear risk	Poor/minimal exclusion criteria; no evidence of publication or funding bias

Gobo-Oliveira 2018

Study characteristics

Methods	• Study design: parallel RCT • Time frame: October 2014 to February 2016 • Duration of study/follow-up: 3 weeks
Participants	• Setting: single centre (inpatients) • Country: Brazil • Inclusion criteria: aged > 18 years, CKD Stage V and on HD for at least 3 months; persistent skin pruritus (any intensity occurring at least 3 times/week and lasting for 30 days or more); no use of topical and/or systemic antipruritic drugs for at least 1 week before the beginning of the study • Number: treatment group 1 (30); treatment group 2 (30) • Mean age ± SD (years): treatment group 1 (64 ± 15); treatment group 2 (59 ± 12) • Sex (M/F): treatment group 1 (15/15); treatment group 2 (19/11) • Relevant comorbidities: not reported • Exclusion criteria: chronic skin disease (allergic, parasitic, or infectious); internal malignancy; use of opioids or corticosteroids
Interventions	Treatment group 1 • Gabapentin (oral): 300 mg, 3 times/week for 3 weeks Treatment group 2 • Dexchlorpheniramine (oral): 6 mg, 3 times/week for 3 weeks
Outcomes	• Pruritus: mean VAS at randomisation and after the intervention • Minimal reporting of adverse effects
Notes	• Conflict of interest: not reported • Funding: "funding for the trial and its publication was provided by FUNADERSP (Sao Paulo, Brazil)" • Correspondence: L. PF Abbade; lfabbade@fmb.unesp.br

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "Randomisation was performed by an individual unrelated to the clinical follow-up using specific software"
Allocation concealment (selection bias)	Low risk	QUOTE: "Randomisation was performed by an individual unrelated to the clinical follow-up using specific software, and the information was held in a sealed opaque envelope containing the name of the therapeutic agent proposed for each group. The randomisation list was under the care of the researchers and patients were labelled as “Group 1” or “Group 2”
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "Both groups were instructed to take one tablet every 12 hours and received two bottles identified as “Home” and “Dialysis”. The “Home” bottle was taken at home by the patient who was directed to take medication twice a day on non-HD days and once daily on HD days. To maintain blinding of the study, for the GABA group, the “Home” bottle contained a placebo identical to the gabapentin capsule, and the medication was stored in the “Dialysis” bottle. The “Dialysis” bottle remained in the Dialysis Unit, and the medication was administered to patients at the end of the session by the responsible technician. Participants and assessors were blinded to the treatment groups"

Gobo-Oliveira 2018 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	QUOTE: "Participants and assessors were blinded to the treatment groups"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Statistical analysis was conducted by intention to treat (ITT). The missing data (dropouts) were replaced by the last recorded values (LOCF) 1 dropout in each arm post randomisation
Selective reporting (reporting bias)	Low risk	Results clearly reported
Other bias	Low risk	No evidence of publication, funding, or other confounding bias

Gunal 2004

Study characteristics	
Methods	• Study design: cross-over RCT • Time frame: not reported • Duration of study/follow-up: 8 weeks
Participants	• Setting: single centre (inpatients) • Country: Turkey • Health status: ESKD on HD; minimum duration of pruritus 8 weeks • Number: 25 • Mean age ± SD: 55 ± 11 years • Sex (M/F): 14/11 • Relevant comorbidities: not reported • Exclusion criteria: concomitant dermatological, liver, or metabolic diseases associated with pruritus.
Interventions	Treatment group • Gabapentin (oral): 300 mg, 3 times/week for 4 weeks Control group • Placebo (oral): 3 times/week for 4 weeks
Outcomes	• Mean pruritis score: VAS daily with mean reported at baseline and end of the treatment period
Notes	• No declared source of funding • Correspondence: Dr. Ali Ihsan Gunal; Firat University, 23200 Elazig, Turkey; igunal@yahoo.com

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	QUOTE: "On a random and blinded basis, patients were assigned to"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgment

Gunal 2004 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "On a random and blinded basis, patients were assigned", "We conducted a double-blind,"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	QUOTE: "double-blinded", "The daily pruritus scores of patients were collected VAS from patient diaries.", "On a random and blinded basis, patients were assigned"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled patients completed the trial and were analysed. Multiple 1 week washout periods preceding intervention and control periods.
Selective reporting (reporting bias)	Unclear risk	All entered patients completed the trial and were analysed Both periods combined reported with mean change and standard deviations reported in full Intervention level data without patient level comparisons provided. Correlation may inflate standard error. Carry-over effects unlikely due to washout periods
Other bias	Low risk	No intervention first group (however 1 week washout). No evidence of publication, funding, or other confounding bias

Hsu 2009

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: 2005 • Duration of study/follow-up: 8 weeks
Participants	• Setting: single centre (outpatients) • Country: Taiwan • Inclusion criteria: ESKD on HD 3 times/week; ongoing pruritus with uraemia as their PCP on their medical record • Number: treatment group (21); control group (20) • Mean age ± SD (years): treatment group (57.1 ± 2.7); control group (66.9 ± 2.1) • Sex (M/F): treatment group (9/12); control group (5/15) • Relevant comorbidities: not reported • Exclusion criteria: dermatological disorders; total bilirubin < 1.0 mg/dL; haematological disorders; organic problems; current use of drugs that might contradict or interfere with the assessments of outcomes
Interventions	Treatment group • Thermal therapy: 40°C thermal therapy with far-infrared rays at the Sanyinjiao acupoint for 15 min, twice/week for 9 weeks Control group • Placebo: plain adhesive patch placed on the same acupoint and routine care; the principal investigator stayed with these patients for 15 min, twice/week for 9 weeks
Outcomes	• Frequency, severity, and location of pruritus: VAS and 5 point Likert scale at 1 and 2 months

Hsu 2009 *(Continued)*

	• Biochemical indicators
Notes	• Correspondence: C.-F. Liu; chifeng@mail1.ntcn.edu.tw

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "A staff team not involved in the trial organized and held the randomisation list and serially numbered envelopes."
Allocation concealment (selection bias)	Low risk	QUOTE: "A staff team not involved in the trial organized and held the randomisation list and serially numbered envelopes. They passed envelopes to the principal investigator after demonstrating that the patient has consented to the trial."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "The non-thermal therapy group received a plain adhesive patch placed on the same acupoint and routine care. The principal investigator stayed with these patients for the same duration as the thermal therapy group." QUOTE: "The staff team was did not know to which treatment group a patient would be allocated. The principal investigator opened envelopes to reveal the study treatment allocation and then administered the intervention."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	QUOTE: "The staff team was did not know to which treatment group a patient would be allocated. The principal investigator opened envelopes to reveal the study treatment allocation and then administered the intervention."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Eight participants (thermal group = 3, non-thermal group = 5) declined or were unable to participate in the study for various reasons (e.g. dermatological disorders and other medical conditions). Not ITT.
Selective reporting (reporting bias)	Low risk	Baseline and results reported for both arms
Other bias	Low risk	No evidence of publication or funding bias

Hui 2011

Study characteristics

Methods	• Study design: parallel RCT • Time frame: December 2008 to December 2009 • Duration of study/follow-up: 1 year
Participants	• Setting: single centre (outpatient) • Country: China • Inclusion criteria: ESKD on regular HD 2 to 3 times/week • Number: treatment group (19); control group (19) • Mean age ± SD (years): treatment group (45 ± 8); control group (44 ± 7) • Sex (M/F): treatment group (10/9); control group (11/8) • Exclusion criteria: serious heart, liver, or lung disease; pregnancy
Interventions	Treatment group

Hui 2011 *(Continued)*

	• High flux HD: 25 to 50 rounds/minute compared to mean rate of blood flow of HD device in the last two sessions before intervention; 3 times/week for 1 year Control group • No change in dialysis
Outcomes	• Skin itching degree score: 10 cm VAS
Notes	• Translated from Chinese

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned by random serial number generated from a random number table
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No change to dialysis for control group
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Low risk	Baseline and final scores fully reported
Other bias	Low risk	No evidence of publication or funding bias

Jiang 2016

Study characteristics

Methods	• Study design: parallel RCT • Time frame: January 2009 to May 2013 • Duration of study/follow-up: 12 weeks
Participants	• Setting: single centre (outpatients) • Country: Iran • Health status: ESKD on HD; aged 20 to 65 years; persistent pruritus for more than 3 months; not having previously been diagnosed with skin disease involving pruritus • Number: treatment group (22); control group (26) • Mean age ± SD (years): treatment group (57.2 ± 18.2); control group (56.4 ± 15.3) • Sex (M/F): treatment group (13/9); control group (15/11) • Relevant comorbidities: not reported

Jiang 2016 *(Continued)*

	• Exclusion criteria: hepatic, cardiopulmonary and uncontrolled psychiatric disease; dermatologic diseases including atopic dermatitis and psoriasis that may cause pruritus; visible infection or having undergone surgical operations on their extremities; received systemic antipruritus therapy more than 1 month or local antipruritus treatment more than 2 weeks
Interventions	Treatment group • High flux HD: Polyilux 140H dialyzer (GAMBRO, Lund, Sweden); The surface area of the high-flux polysulfone membrane was 1.4 m^2 and the ultrafiltration coefficient was 60.0 mL/h/mmHg; 3 times/week for 12 weeks Control group • Normal flux dialysis: CA-HP170 dialyzer (Baxter, Deerfield, USA). The surface area of the polysulfone membrane was 1.7 m^2 (GAMBRO, Lund, Sweden) and the ultrafiltration coefficient was 57.0 mL/h/mmHg for 12 weeks
Outcomes	• Pruritus severity: VAS and modified Duo VAG scale • QoL
Notes	• No declared conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "randomly allocated to two groups with the aid of ClinStat software"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% dropout in both groups and balanced
Selective reporting (reporting bias)	Unclear risk	All results clearly reported
Other bias	Low risk	No evidence for publication or funding bias

Ko 2011

Study characteristics

Methods	• Study design: parallel RCT • Time frame: June 2007 to July 2009

Ko 2011 *(Continued)*

	• Duration of study/follow-up: 12 weeks
Participants	• Setting: single centre (outpatients) • Country: Taiwan • Inclusion criteria: CKD 4-5; minimum duration of uraemic pruritus 2 months (VAS > 5); if on dialysis Kt/V < 1.4 • Number: treatment group (11); control group (10) • Mean age ± SD (years): treatment group (60.9 ± 11.5); control group (63.2 ± 11.3) • Sex M/F: (6/5); (5/5) • Relevant comorbidities: treatment group (cardiovascular disease (8); DM (4); atopic diathesis (10); control group (cardiovascular disease (4); DM (4); atopic diathesis (2)) • Exclusion criteria: pregnant or breastfeeding; those with a history of photosensitivity
Interventions	Treatment group • UV-B therapy: ~ 200 mJ/cm^2; 3 times/week for 6 weeks • 24 UVB lamps (TL 100W/01 311NB UVB) for 15 minutes Control group • UV-A therapy:~ 1 to 6 J/cm^2; 3 times/week for 6 weeks • 24 UV-A lamps (F72T12 BL9 HO UVA)
Outcomes	• Pruritus intensity: VAS
Notes	• Correspondence: Hsien-Ching Chiu or Shiou-Hwa Jee; email: hcchiu1003@ntu.edu.tw; shiouhwa@ntu.edu.tw

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "The enrolled patients were randomly assigned to the treatment and control groups, with an allocation ratio of 1: 1, according to a sequence of computer-generated randomised codes"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	QUOTE: "The control group received time-matched exposures to long- wave UVA. The doses of UVA were approximately 1– 6 J cm^{-2}, which was an appropriate control in this study." "Single blinded"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	QUOTE: "Single blinded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	An allocation ratio of 1:1 of is reported
Selective reporting (reporting bias)	Low risk	Baseline and results reported for both arms
Other bias	Low risk	No evidence of publication or funding bias

Kumagai 2010

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: not reported • Duration of study/follow-up: 3 weeks
Participants	• Setting: multicentre (73 sites) (inpatients) • Country: Japan • Inclusion criteria: aged ≥ 20 years; ESKD on HD; minimum duration of pruritus 1 year • Number: treatment group 1 (113); treatment group 2 (113); control group (111) • Mean age ± SD (years): treatment group 1 (59.6 ± 11.5); treatment group 2 (61.0±11.4); control group (59.6±11.8) • Sex: treatment group 1 (93/21); treatment group 2 (85/27); control group (89/22) • Relevant comorbidities: not reported • Exclusion criteria: responding adequately to systemic treatment (with oral or injectable prescription antihistamines or anti-allergy drugs) administered for 2 weeks or longer; or to local treatment (with prescription drugs approved for the treatment of pruritus or moisturizing agents prescribed by physicians)
Interventions	Treatment group 1 • Nalfurafine (oral): 5 µg once/day for 2 weeks Treatment group 2 • Nalfurafine (oral): 2.5 µg once/day for 2 weeks Control group • Placebo (oral): once/day for 2 weeks
Outcomes	• Pruritus severity: VAS
Notes	• No declared source of funding • Hiroo Kumagai; E-mail: hkumagai@ndmc.ac.jp

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "receive 5 µg, 2.5 µg nalfurafine or a placebo using a variable size permuted block design stratified by centre"
Allocation concealment (selection bias)	Unclear risk	QUOTE: "variable size permuted block design" this implies the assignments are coded
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "The patients took the soft capsules containing the drug or placebo once daily"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	QUOTE: "double blinded". Patient's directly recorded their VAS scores.

Kumagai 2010 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	QUOTE: "Each arm had 2-3 patients discontinue due to adverse effects. 1 patient in each arm who did not received any treatment were not analysed." QUOTE: "The full analysis set (FAS), defined as all patients who were randomised and received at least one dose of study drug and were as close as possible to the intention-to-treat ideal, was chosen for examining the primary end point." - Few dropouts and followed ITT
Selective reporting (reporting bias)	Low risk	Baseline and post interventions results fully reported
Other bias	Low risk	No evidence for publication, funding, or other confounding bias

Kyriazis 2000

Study characteristics	
Methods	• Study design: triple cross-over RCT • Time frame: not reported • Duration of study/follow-up: 12 days
Participants	• Setting: single centre (outpatients) • Country: Greece • Inclusion criteria: ESKD on HS with intermittent uraemic pruritus • Number: 4 • Mean age ± SD: 69 ± 11 years • Sex: all male • Relevant comorbidities: not reported • Exclusion criteria: not reported
Interventions	Treatment group 1 • Ca dialysate: 1.0 mmol/L, 4 sessions of HD Treatment group 2 • Ca dialysate: 1.25 mmol/L, 4 sessions of HD Treatment group 2 • Ca dialysate: 1.75 mmol/L, 4 sessions of HD
Outcomes	• Pruritus score (unspecified scale)
Notes	• No declared conflicts of interest • John Kyriazis, MD; General Hospital of Chios, Dialysis Unit, Chios 82100 (Greece), Tel: +30 271 44312, E-Mail: jks@athena.compulink.gr

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	QUOTE: "randomised"

Kyriazis 2000 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the trial and are reported on
Selective reporting (reporting bias)	High risk	Pre and post intervention scores not reported
Other bias	Unclear risk	No female participants; no evidence of publication or funding bias

Legroux-Crespel 2004

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: June to August 2002 • Duration of study/follow-up: 2 weeks
Participants	• Setting: multicentre (4 sites) (inpatients) • Country: France • Inclusion criteria: pruritus (1 month or more) in patients aged > 18 years with ESKD on HD • Number: treatment group 1 (26); treatment group 2 (26) • Mean age ± SD: 62.6 ± 15.8 years • Sex (M/F): 63%/37% • Relevant comorbidities: nephroangiosclerosis (12); undetermined chronic glomerulonephritis (10); chronic interstitial nephritis (8), diabetic kidney disease (5); renal polycytosis (4); IgA chronic glomerulonephritis (4); rapidly progressive glomerulonephritis (3), membranoproliferative glomerulonephritis (2); focal and segmentary hyalinosis (2); uraemic and haemolytic syndrome (1); Henoch-Schönlein purpura (1); vesicoureteric reflux nephropathy (1); diffuse proliferative extracapillary glomerulonephritis (1); amyloidosis and bilateral renal dysplasia (1) • Exclusion criteria: all other possible causes of pruritus; pregnancy; lactation; hypersensitivity to naltrexone or loratadine; dependency on opioids; severe liver insufficiency
Interventions	Treatment group 1 • Naltrexone (oral): 50 mg, once/day for 2 weeks Treatment group 2 • Loratadine (oral): 10 mg, once/day for 2 weeks
Outcomes	• Intensity of pruritus: VAS as means at baseline and weekly • Adverse events

Legroux-Crespel 2004 *(Continued)*

Notes	• No declared source of funding • Correspondence: Prof. Laurent Misery, Department of Dermatology, University Hospital, 5, avenue Foch FR–29609 Brest Cedex (France); Tel. +33 298 22 33 15, Fax +33 298 22 33 82, E-Mail laurent.misery@chu-brest.fr

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "This was a randomised study (drawing of lots)"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. Likely not blinded. No discussion for treatment concealment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear number of dropouts, at least 10
Selective reporting (reporting bias)	High risk	Missing raw data (No standard deviations for either group or baseline scores score for the natrexone group reported)
Other bias	High risk	Conflicting results and arbitrary definitions of improvement; no evidence of publication or funding bias

Li 2017a

Study characteristics

Methods	• Study design: parallel RCT • Time frame: January 2009 • Duration of study/follow-up: 8 weeks
Participants	• Setting: single centre (outpatients) • Country: China • Inclusion criteria: ESKD on HD; uraemic pruritus "who have received a variety of blood purification treatments for more than 1 month (including HDF, HFHD, and HA130-HP), and had small improvements on skin itching symptoms or frequent attacks" • Number: treatment group 1 (30); treatment group 2 (30); control group (30) • Mean age ± SD (years): treatment group 1 (53.32 ± 12.21); treatment group 2 (54.17 ± 13.24); control group (55.37 ± 15.38) • Sex (M/F): not reported • Relevant comorbidities: not reported • Exclusion criteria: systemic diseases (liver, gallbladder disease, allergies, asthma, and tumours); skin diseases (psoriasis and skin tinea diseases); metabolic diseases; contraindications to haemoperfusion

Li 2017a *(Continued)*

Interventions	Treatment group 1 • Regular HD + haemoperfusion with HA130-RHA (Zhuhai Jafron Biotechnology Inc.): 3 times/week for 8 weeks Treatment group 2 • Regular HD + haemoperfusion with HA330-RHA (Zhuhai Jafron Biotechnology Inc.): 3 times/week for 8 weeks Control group • Regular HD: 3 times/week for 8 weeks
Outcomes	• Pruritus: VAS and modified Duo score
Notes	• No declared conflicts of interest • Correspondence: Jin-Wen Wang, Department of Kidney Disease, Yan'an, Hospital Affiliated to Kunming Medical University, Nephrology, No. 245 people's east road, Kunming 650051, China (e-mail: drwang_16@163.com)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patient randomly selected letters
Allocation concealment (selection bias)	Low risk	QUOTE: "Sealed letters"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants aware of their intervention
Blinding of outcome assessment (detection bias) All outcomes	High risk	Participants aware of their intervention
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Specified pre and post intervention scores not reported, but some surrogate statistics are
Selective reporting (reporting bias)	Low risk	< 10% dropouts post randomisation
Other bias	Unclear risk	Patients recruited mid study to replace all dropout as specified in their protocol

Lin 2012

Study characteristics

Methods	• Study design: quasi-RCT • Time frame: not reported

Lin 2012 *(Continued)*

	• Duration of study/follow-up: 3 weeks
Participants	• Setting: single centre • Country: Taiwan • Inclusion criteria: currently undergoing HD treatment initiated at least 3 months earlier, aged ≥ 18 years; complaint of at least 3 episodes of pruritus in the past 2 weeks; no improvement for at least 1 month after taking medications; ability to communicate • Number: treatment group 1 (30); treatment group 2 (31); control group (32) • Mean age ± SD: 60.9 ± 12.7 years (no means for subgroups reported) • Sex: treatment group 1 (17/13); treatment group 2 (16/15); control group (22/10) • Relevant comorbidities (treatment group 1/treatment group 2/control group): hypertension(26/26/22); DM (15/13/12); heart disease (11/8/8); dyslipidaemia (5/3/0); gout (3/6/2); gastric ulcer (1/3/5) • Exclusion criteria: children; signs of oedema
Interventions	Treatment group 1 • Chilled baby oil (10C to 15C): 15 minutes of application to affected areas at least once/day (average 2.80 times/day) for 3 weeks Treatment group 2 • Unchilled baby oil (24C to 26C): 15 minutes of application to affected areas at least once/day (average 2.87 times/day) for 3 weeks Control group • Usual care
Outcomes	• Pruritus: Itch Severity Scale (ISS) at baseline and postintervention (3 weeks)
Notes	• No declared source of funding • Correspondence: Hsin-Tien Hsu, Assistant Professor, College of Nursing, Kaohsiung Medical University, 100, Shih-Chuan 1st Road, Kaohsiung 807, Taiwan. Telephone: +886 7 3121101 ext. 2630. E-mail: hthsu@kmu.edu.tw

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	QUOTE: "All qualified participants were recruited. Those currently receiving haemodialysis treatment every Monday, Wednesday and Friday were enrolled in experimental group 1; those currently receiving haemodialysis treatment on Tuesday, Thursday and Saturday, were enrolled in experimental group 2. The control group consisted of patients randomly selected from the above two groups." Quasi-RCT
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias)	High risk	Doctor administered questionnaire with no blinding reported

Lin 2012 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 skin rash, privacy concerns and hospitalisation. Unclear which treatment arms they were in
Selective reporting (reporting bias)	Low risk	Change in pruritus and baseline pruritus reported
Other bias	Unclear risk	Poor exclusion criteria. Blinding likely not possible as intended for intervention type. No evidence of publication or funding bias

Mahmudpour 2017

Study characteristics

Methods	• Study design: parallel RCT • Time frame: April to August 205 • Duration of study/follow-up: 30 days
Participants	• Setting: multicentre (3 sites) (inpatients) • Country: Iran • Inclusion criteria: patients aged > 18 years with ESKD on HD suffering from pruritus during the past 3 months that, despite consumption of antipruritic medications, had not experienced proper response to medications • Number (randomised/analysed): treatment group (40/36); control group (40/37) • Mean age ± SD: 53.3 ± 15.8 years (no means for subgroups reported) • Sex: not reported • Relevant comorbidities: not reported • Exclusion criteria: < 3 months history of pruritus; Kt/V < 1.2; dermatologic diseases; malignancies; cholestatic diseases; active infection or infection with hepatitis B or C virus; Hb < 10 g/dL
Interventions	Treatment group • Montelukast (oral): 10 mg/day for 30 days Control group • Placebo (oral): daily for 30 days
Outcomes	• Pruritus: 10 cm VAS, 33-point Duo score
Notes	• No declared source of funding • Mohammad Mehdi Sagheb, MD Department of Nephrology, Namazi Hospital, Shiraz University of Medical Sciences, Shiraz, Iran E-mail: saghebf@gmail.com

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "...enrolled in the study and based on block randomization method, were randomised into 2 groups of 40 participants"
Allocation concealment (selection bias)	Low risk	QUOTE: "All medication and placebo tablets were similar in size, shape, weight, color, and package. Clinical investigators, laboratory personnel, and

Mahmudpour 2017 *(Continued)*

		patients were all masked to the treatment assignment and code breaking was done at the end of study"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "All medication and placebo tablets were similar in size, shape, weight, color, and package. Clinical investigators, laboratory personnel, and patients were all masked to the treatment assignment and code breaking was done at the end of study"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	QUOTE: "All medication and placebo tablets were similar in size, shape, weight, color, and package. Clinical investigators, laboratory personnel, and patients were all masked to the treatment assignment and code breaking was done at the end of study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% dropout in each arm, roughly equal, with explanation
Selective reporting (reporting bias)	Low risk	Outcomes clearly reported
Other bias	Low risk	No evidence of publication, funding, or other confounding bias

Makhlough 2010

Study characteristics	
Methods	• Study design: cross-over RCT • Time frame: July 2007 to February 2008 • Duration of study/follow-up: 8 weeks (2 x 3-week treatment periods including 2-week washout)
Participants	• Setting: single centre • Country: Iran • Inclusion criteria: patients with ESKD on HD with persistent pruritus after 3 months of treatment with other drugs, reported subjectively by the patient • Number: 34 • Mean age ± SD: 57.0 ±18.6 years • Sex (M/F): 14/20 • Relevant comorbidities: not reported • Exclusion criteria: history of systemic therapy for pruritus started in the past month or local therapy started in the past 2 weeks (e.g. immunosuppressive drugs, cholestyramine, capsaicin, opioid agonists and antagonists, antiserotonin, glucocorticoids, thalidomide, sedative drugs and ultraviolet B); hepatobiliary diseases (based on history and liver function tests); malignancies; hyperparathyroidism (based on plasma parathyroid hormone), dermatitis, dermatologic diseases (e.g. scabies and pediculosis, according to dermatologist consultant); hyperphosphataemia (serum phosphorous level > 5.5 mg/dL)
Interventions	Treatment group • Capsaicin ointment (topical): 0.03% rubbed on pruritis patches 4 times/day for 4 weeks Control group • Matched placebo (topical): rubbed on pruritis patches 4 times/day for 4 weeks
Outcomes	• Severity of pruritus: Mean Modified Duo scale at baseline and weekly

Makhlough 2010 *(Continued)*

	• Adverse effects: "Skin burning"
Notes	• No declared conflict of interest • Correspondence to: Atieh Makhlough, MD, Department of Nephrology, Imam Khomeini Hospital, Mazandaran University of Medical Sciences, Sari, Iran Tel: +98 151 223 4506 Fax: +98 151 223 4506 E-mail: makhlough_a@yahoo.com

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "Randomly assigned by lottery into 2 groups"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "Double blind" QUOTE: "The placebo was prepared in a same size and colour packages as Capsian 0.03% ointment tubes."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	QUOTE: "Double blind" QUOTE: "The placebo was prepared in a same size and colour packages as Capsian 0.03% ointment tubes."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All entered patients completed the trial and were analysed
Selective reporting (reporting bias)	Low risk	Baseline and results reported for both arms
Other bias	Low risk	No evidence of publication, funding, or other confounding bias

Mapar 2015

Study characteristics

Methods	• Study design: pilot parallel RCT • Time frame: November 2011 to February 2012 • Duration of study/follow-up: 4 weeks
Participants	• Setting: single centre (outpatients) • Country: Iran • Inclusion criteria: aged between 23 to 79 years with ESKD on HD and having pruritus for more than 6 weeks • Number (randomised/analysed): treatment group (20/18); control group (20/18) • Mean age ± SD (years):not reported • Sex (M/F): 25/11 • Relevant comorbidities: hypertension (9); DM (17); hydronephrosis (1); urological problems (1); unknown aetiology (12)

Mapar 2015 *(Continued)*

	• Exclusion criteria: calcium phosphorous product > 70; medical history of systemic diseases such as malignancy; liver disease; under treatment with steroids or opiate analgesics
Interventions	Treatment group • Zinc sulfate (oral): 220 mg/day for 4 weeks Control group • Placebo (oral): daily for 4 weeks
Outcomes	• Severity of pruritus: Duo score • Adverse effects
Notes	• No declared conflicts of interest • N. Pazyar, Department of Dermatology, Aza- degan Street, Imam Hospital, Ahvaz, Iran. E-mail: dr.pazyar@gmail.com

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "randomised, triple-blind study"
Allocation concealment (selection bias)	Unclear risk	QUOTE: "randomised, triple-blind study"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "randomised, triple-blind study"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	QUOTE: "randomised, triple-blind study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% dropouts per arm with explanation
Selective reporting (reporting bias)	Low risk	Clear results
Other bias	Low risk	No evidence of publication, funding, or other confounding bias

Marin 2013

Study characteristics

Methods	• Study design: parallel RCT • Time frame: not reported • Duration of study/follow-up: 12 weeks
Participants	• Setting: single centre • Country: Mexico

Marin 2013 *(Continued)*

	• Inclusion criteria: aged 18 to 70 years on APD and having pruritus without alternative cause for more than 3 months • Number: treatment group 1 (18); treatment group 2 (18) • Mean age ± SD (years): treatment group 1 (56.7 ± 12.4); treatment group 2 (48.5 ± 14.6) • Sex (M/F): treatment group 1 (22/8); treatment group 2 (21/9) • Exclusion criteria: pre-existing skin or liver disease, or requiring treatment of Gabapentin for alternative reasons such as diabetic neuropathy
Interventions	Treatment group 1 • Gabapentin (oral): 300 mg every 24 hours for 9 weeks Treatment group 2 • Loratadine (oral): 10 mg every 24 hours for 9 weeks
Outcomes	• Pruritus: VAS • Adverse effects
Notes	• Government funded • Abstract-only publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A simple randomization will be carried out by computer using the medcalc software"
Allocation concealment (selection bias)	High risk	"open, comparative clinical trial"
Blinding of participants and personnel (performance bias) All outcomes	High risk	"open, comparative clinical trial"
Blinding of outcome assessment (detection bias) All outcomes	High risk	"open, comparative clinical trial"
Incomplete outcome data (attrition bias) All outcomes	Low risk	5% attrition rate (2 drop out in the gabapentin group and none in the Loratidine group)
Selective reporting (reporting bias)	Low risk	All results fully and clearly reported
Other bias	Low risk	"The study is financed by the Hospital de Concentración ISSEMyM Satélite" No evidence of publication or funding bias

Mettang 1997

Study characteristics

Mettang 1997 *(Continued)*

Methods	• Study design: parallel RCT • Time frame: not reported • Duration of study/follow-up: 16 weeks
Participants	• Setting: single centre (outpatients) • Country: Germany • Inclusion criteria: ESKD on HD and 4 weeks of documented uraemic pruritus • Number: treatment group (9); control group (8) • Mean age ± SD (years): treatment group (64.6 ± 14.2); control group (59.9 ± 13.7) • Sex (M/F): treatment group (3/9); control group (3/5) • Relevant comorbidities: not reported • Exclusion criteria: DM; malignant disease; autoimmune disease necessitating immunosuppressive or steroid therapy
Interventions	Treatment group • L-carnitine (IV): 10 mg/kg, once/dialysis session for 16 weeks Control group • Placebo (IV): once/dialysis session for 16 weeks
Outcomes	• Pruritus score: VAS from 0-6 in daily diary. Baseline and final scores reported
Notes	• "Supported in part by research grants from Fresenius AG, Oberursel; the Khalil Foundation; the Robert-Bosch Foundation, Stuttgart; and Fa Medice, Iserlohn, Germany" • Dr T. Mettang; Robert-Bosch-Krankenhaus, Auerbachstrasse 110 D-70376 Stuttgart, Germany

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "A Double-Blind randomised Trial"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	QUOTE: "Double-Blind"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	QUOTE: "Double-Blind" and patient recorded diary
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, but with implication of no dropouts
Selective reporting (reporting bias)	Low risk	Baseline and postintervention results reported
Other bias	Unclear risk	QUOTE: "Supported in part by research grants from Fresenius AG, Oberursel; the Khalil Foundation; the Robert-Bosch Foundation, Stuttgart; and Fa Medice, Iserlohn, Germany"

Mirnezami 2013

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: 2 weeks • Duration of study/follow-up: 2 weeks
Participants	• Setting: single centre • Country: Iran • Inclusion criteria: patients with CKD undergoing HD; minimum age 18 years. • Number: 70 • Mean age ± SD: not reported • Sex: not reported • Relevant comorbidities not reported • Exclusion criteria: Patients with a history of skin or metabolic disease causing itching; Patients who received antipruritic medications two weeks before; pregnant women
Interventions	Treatment group 1 • Ondansetron (oral): 8 mg 3 times/day Treatment group 2 • Loratidine (oral): 10 mg, twice/day
Outcomes	• Change in 10 cm VAS scores after treatment with ondansetron and loratadine
Notes	• No declared source of funding

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	QUOTE "randomised"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	QUOTE "Double Blinded"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	QUOTE "Double Blinded"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Change in pruritus and baseline pruritus reported
Other bias	Unclear risk	Abstract only

Mohamed 2012

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: not reported • Duration of study/follow-up: 6 months
Participants	• Setting: single centre (inpatients) • Country: Egypt • Inclusion criteria: ESKD on HD; "Those who were complaining of severe pruritus as scored using the Dermatological Life Quality Index (DLQI)" • Number: treatment group (25); control group (20) • Mean age ± SD (years): not reported • Sex: not reported • Relevant comorbidities: not reported • Exclusion criteria: not reported
Interventions	Treatment group • Sodium thiosulfate (IV): 12.5 mg, once/dialysis session for 6 months Control group • Placebo (IV): once/dialysis session for 6 months
Outcomes	• Severe pruritus: VAS daily at baseline and study completion
Notes	• Abstract-only publication • No declared source of funding • Walid Mohamed Alexandria; University Student Hospital, Elshatby, Alexandria, Egypt

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "Randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	High risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement

Mohamed 2012 *(Continued)*

Selective reporting (reporting bias)	High risk	No numeric results
Other bias	Unclear risk	Abstract-only publication; poorly explained inclusion/exclusion criteria

Mojgan 2017

Study characteristics

Methods	• Study design: cross-over RCT • Time frame: not reported • Duration of study/follow-up: 4 weeks + "washout" + 4 weeks
Participants	• Setting: single centre (inpatients) • Country: Iran • Inclusion criteria: ESKD on HD with uraemic pruritus • Number: 20 • Mean age ± SD (years): not reported • Sex: not reported • Relevant comorbidities: not reported • Exclusion criteria: not reported
Interventions	Treatment group • Fish oil (oral): 1 g, 3 times/day for 4 weeks Control group • Placebo (oral): 3 times/day for 4weeks
Outcomes	• Aggregate "Pruritus score" change
Notes	• Abstract-only publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "randomised"
Allocation concealment (selection bias)	Unclear risk	QUOTE: "Double blind"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	QUOTE: "Double blind"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	QUOTE: "Double blind"
Incomplete outcome data (attrition bias)	Unclear risk	Unclear dropout rate

Mojgan 2017 *(Continued)*
All outcomes

Selective reporting (reporting bias)	High risk	Only group means and a nonspecific P value reported
Other bias	Unclear risk	Abstract-only publication; insufficient information to permit judgement

Murphy 2003

Study characteristics

Methods	• Study design: cross-over RCT • Time frame: not reported • Duration of study/follow-up: 6 weeks (2 x 1 week washout + 2 week trial)
Participants	• Setting: multicentre (2 sites) (inpatients) • Country: UK • Inclusion criteria: ESKD on HD; minimum duration of pruritus 8 weeks • Number: treatment first group (14); control first group (10) • Median age: 59 years • Sex (M/F): 20/4 • Relevant comorbidities: not reported • Exclusion criteria: concomitant dermatological disease associated with pruritus as assessed by a dermatologist or another metabolic cause of itch; history of poor compliance; pregnant; < 18 years
Interventions	Treatment group • Ondansetron (oral): 8 mg, 3 times/day for 2 weeks Control group • Placebo (oral): 3 times/day for 2 weeks
Outcomes	• Pruritus: VAS twice daily reported at baseline and weekly
Notes	• This work was supported by a grant from the Northern and Yorkshire NHS Executive • Correspondence: Dr Michelle Murphy; drmichellemurphy@eircom.net

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "On a random basis, 24 patients were blindly allocated..."
Allocation concealment (selection bias)	Low risk	QUOTE: "On a random basis, 24 patients were blindly allocated..."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "... were blindly allocated to the ondansetron-placebo sequence and 10 to the placebo-ondansetron sequence"
Blinding of outcome assessment (detection bias)	Low risk	QUUOTE: "Double blind", VAS directly recorded by patients. Investigator independent from implementation

Murphy 2003 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	High risk	Not ITT. ~25% attrition. Non-compliance and complications partially addressed. Cross-over design likely limits the severity of the bias
Selective reporting (reporting bias)	Low risk	VAS from patient diaries. All baselines and results reported
Other bias	Low risk	No evidence of publication, funding, or other confounding bias

Naghibi 2007

Study characteristics

Methods	• Study design: cross-over RCT • Time frame: not reported • Duration of study/follow-up: 9 weeks (1 week washout + 4 week trial for each ordering)
Participants	• Setting: single centre (inpatients) • Country: Iran • Inclusion criteria: ESKD on HD with uraemic pruritus • Number: 20 • Mean age ± SD (years): not reported • Sex (M/F): not reported • Relevant comorbidities: not reported "Gabapentin therapeutic response was not affected by age, sex, dialysis duration, cause of ESRD and pruritus duration" • Exclusion criteria: referenced, but not explicitly stated
Interventions	Treatment group • Gabapentin (oral): 4 weeks (dose and frequency not reported) Control group • Placebo (oral): 4 weeks (dose and frequency not reported)
Outcomes	• The mean difference of pruritus score (VAS) before and after treatment • Adverse effects with incomplete reporting ("well tolerated")
Notes	• Abstract-only publication • No declared conflicts of interest • Correspondence: Dr Massih Naghibi, Department of Internal Medicine, Imam-Reza Hospital, Mashad University of Medical Sciences (MUMS), Mashhad, Khorasan, Iran

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "On a random and blinded basis"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

Naghibi 2007 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "On a random and blinded basis"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	QUOTE: "On a random and blinded basis"
Incomplete outcome data (attrition bias) All outcomes	Low risk	QUOTE: "All of the patients completed the study"
Selective reporting (reporting bias)	Low risk	The mean difference of pruritus score (VAS) before and after treatment was fully reported. One week washout in between all interventions and controls. Carry-over effects unlikely
Other bias	Unclear risk	Abstract-only publication; group level data without patient level comparisons provided; correlation may inflate SE

Naini 2007

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: not reported • Duration of study/follow-up: 4 weeks
Participants	• Setting: single centre (inpatients) • Country: Iran • Inclusion criteria: on maintenance HD twice a week for at least 3 months; minimum duration of pruritus 8 weeks • Number: 34 total divided into 2 groups (numbers per group not reported) • Mean age ± SD: 62 ± 10 years (groups not reported) • Sex (M/F): 16/18 (groups not reported) • Relevant comorbidities: not reported • Exclusion criteria: hyperparathyroidism; hyperphosphataemia; anaemia (Hb < 7 g/dL); dermatological disease
Interventions	Treatment group • Gabapentin (oral): 400 mg twice/week for 4 weeks Control group • Placebo (oral): twice/week for 4 weeks
Outcomes	• Pruritus score: VAS twice daily • Adverse effects
Notes	• No declared source of funding • Dr. Afsoon Emami Naini, Associate Professor, Department of Nephrology Noor Hospital Isfahan University of Medical Sciences, Isfahan, Iran Emaminaini_afsoon@yahoo.com

Naini 2007 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "The patients were randomly allocated to receive either gabapentin 400 mg or placebo"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "to prepare the placebo, we emptied gabapentin capsules and refilled them with flour, thus making them indistinguishable"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	QUOTE: "double blind" VAS from patient diaries. Investigator independent
Incomplete outcome data (attrition bias) All outcomes	Low risk	All entered patients completed the trial and were analysed
Selective reporting (reporting bias)	Low risk	Baseline and mean decreases reported
Other bias	Low risk	No evidence of publication, funding, or other confounding bias

Najafabadi 2012

Study characteristics

Methods	• Study design: parallel RCT • Time frame: 2008 to 2009 • Duration of study/follow-up: 2 months treatment + 1 month follow-up
Participants	• Setting: multicentre (number of sites not reported) (outpatients) • Country: Iran • Inclusion criteria: maintenance HD > 8 weeks; minimum duration of pruritus 8 weeks • Number: treatment group (20); control group (20) • Mean age ± SD (years): treatment group (53.4 ± 14.5); control group (57.6 ± 16.1) • Sex (M/F): treatment group (15/5); control group (14/6) • Relevant comorbidities (treatment group/control group): DM (7/8); hypertension (3/4) • Exclusion criteria: skin problems other than uraemic pruritus; sensitivity to zinc sulfate; kidney transplant during the study; presence of any co-morbidities; administration of any oral anti-pruritic drugs; anaemia; hyperparathyroidism (PTH > 300 pg/mL or phosphorus > 7 mg/dL); increased alkaline phosphatase
Interventions	Treatment group • Zinc sulfate (oral): 200 mg, twice/day for 2 months Control group • Placebo (oral): twice/day for 2 months

Najafabadi 2012 *(Continued)*

Outcomes	• Pruritus: mean VAS at baseline and every 2 weeks • Adverse effects nonspecific ("minimal")
Notes	• No declared conflicts of interest • Dr Amir Hosein Davarpanah Jazi, Medical Education Research Center, Isfahan University of Medical Sciences, Isfahan 8174673461, Iran. Email: davarpanah@edc.mui.ac.ir

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "The patients were then randomly assigned into treatment and placebo groups."
Allocation concealment (selection bias)	Low risk	QUOTE: "At the end of the study the drug and placebo groups were determined by decoding."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "Double blind", "while the other group received a similar shaped and coloured capsule which was a placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	QUOTE: "Neither the patients nor the physicians had any knowledge of the group to which patients were assigned. The patients were assigned codes, and at the end of the study the drug and placebo groups were determined by decoding."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled patient completed the trial and were analysed
Selective reporting (reporting bias)	Low risk	Baseline and postintervention results clearly recorded
Other bias	Low risk	No evidence of publication, funding, or other confounding bias

Nakhaee 2015

Study characteristics

Methods	• Study design: cross-over RCT • Time frame: not reported • Duration of study/follow-up: 6 weeks
Participants	• Setting: single centre (inpatients) • Country: Iran • Inclusion criteria: HD at least twice weekly, and experienced uraemic pruritus for at least 2 weeks • Number: 23 • Mean age ± SD: 57.04 ± 12.20 years • Sex (M/F): 17/6 • Relevant comorbidities: not reported • Exclusion criteria: history of dermal or nondermal pruritic diseases such as atopic dermatitis; chronic hepatic disorder, acquired immune deficiency syndrome, and polycythaemia vera, according to their charts and examination by specialists; chronic dermal inflammatory disorders or known aller-

Nakhaee 2015 *(Continued)*

	gy records; pregnant or breast-feeding; unwillingness to participate in the study; treatment complications such as allergic reaction to vinegar or Avena sativa; kidney transplantation
Interventions	Treatment group 1 • Avena sativa (topical): variable dose, twice/day for 2 weeks Treatment group 2 • Dilute vinegar (topical): 30 mL synthetic white vinegar 5% in 500 ml of water, twice/day for 2 weeks Treatment group 3 • Hydroxyzine (oral): 10 mg/day, for 2 weeks
Outcomes	• Pruritus: 10 cm VAS
Notes	• No declared source of funding • Ahmad Nasiri, PhD, Health Qualitative Research Center, Birjand University of Medical Sciences, Birjand, Iran Tel: +98 563 239 5353 Fax: +98 563 2440550 E-mail: nasiri2006@bums.ac.ir

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: Assigned by random numbers to 3 groups (two with 8 patients and one with 9). The CONSORT flowchart that describes the progress of the patients through the trial"
Allocation concealment (selection bias)	Unclear risk	QUOTE: "Assigned by random numbers to 3 groups (two with 8 patients and one with 9). The CONSORT flowchart that describes the progress of the patients through the trial"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Topical and scented intervention versus oral
Blinding of outcome assessment (detection bias) All outcomes	High risk	Topical and scented intervention versus oral
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 dropouts post randomisation due to kidney transplantation
Selective reporting (reporting bias)	High risk	Only 3-day washout. Intervention level data without patient level comparisons provided
Other bias	Low risk	No evidence of publication or funding bias

Nasrollahi 2007

Study characteristics

Methods	• Study design: cross-over RCT • Time frame: November 2005 to November 2006

Nasrollahi 2007 *(Continued)*

	• Duration of study/follow-up: 20 days + 14 days washout + 20 days
Participants	• Setting: multicentre (5 sites) • Country: Iran • Inclusion criteria: aged 20 to 85 years; minimum duration of pruritus > 3 months with sleep disturbances and daily activity interference. • Number: 16 • Mean age: men (65 years); women (63 years) • Sex (M/F): 10/6 • Relevant comorbidities: not reported • Exclusion criteria: Kt/V < 1.2; no CKD-related pruritis
Interventions	Treatment group • Montelukast (oral): 10 mg/day for 20 days Control group • Placebo (oral): daily for 20 days
Outcomes	• Mean change in pruritus score: Duo score "regularly"
Notes	• No declared source of funding • Correspondence: Farshid Haghverdi, MD, Department of Internal Medicine, Shohada-e-Tajrish Hospital, Tajrish Sq, Tehran, Iran Tel: +98 912 186 4403 E-mail: farshid_430@yahoo.com

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "The patients were randomly divided into groups 1 and 2"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	QUOTE: "single-blind"
Blinding of outcome assessment (detection bias) All outcomes	High risk	QUOTE: "single-blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Anaemia from myelodysplasic syndrome in montelukast arm (1); death but to myocardial infarction in placebo (1) Not ITT, but followed the Good Clinical Practices guidelines in RCTs which recommended including the MI patient and excluding the myelodysplasic patient
Selective reporting (reporting bias)	Unclear risk	Only percent changes recorded with no baseline Intervention level data without patient level comparisons provided Carry-over effects unlikely due to washout periods
Other bias	Low risk	No evidence of publication, funding, or other confounding bias

Nofal 2016

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: March 2013 to March 2014 • Duration of study/follow-up: 1 month
Participants	• Setting: single centre (inpatients) • Country: Egypt • Inclusion criteria: undergoing HD with uraemic pruritus for at least 3 months and not relieved by traditional therapy • Number: treatment group (27); control group (27) • Mean age ± SD (years): treatment group (51.5 ± 9.96); control group (52.15 ± 9.94) • Sex (M/F): treatment group (23/4); control group (18/9) • Relevant comorbidities: not reported • Exclusion criteria: Hb < 7 g/dL; hyperphosphataemia; hypercalcaemia; history of systemic disorders causing pruritus other than kidney failure; concomitant dermatological disorders associated with pruritus
Interventions	Treatment group • Gabapentin (oral): 300 mg/day for 1 month Control group • Placebo (oral): daily for 1 month
Outcomes	• Pruritus: VAS weekly, 5-D scale • Adverse effects
Notes	• No declared source of funding • Eman Nofal emannofal@gmail.com Department of Dermatology and Venereology, Faculty of Medicine, Zagazig University, Zagazig, 44516, Egypt

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "Randomization was done by random number list"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	QUOTE: "single-blinded trial"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	QUOTE: "single-blinded trial"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised patient analysed

Nofal 2016 *(Continued)*

Selective reporting (reporting bias)	Low risk	All results clearly reported
Other bias	Low risk	No evidence for publication, funding, or other confounding bias

Noshad 2011

Study characteristics

Methods	• Study design: parallel RCT • Time frame: 12 month period • Duration of study/follow-up: 4 weeks
Participants	• Setting: single centre (inpatients) • Country: Iran • Inclusion criteria: patients with ESKD on HD with uraemic pruritus • Number: treatment group (20); control group (20) • Mean age ± SD (years): treatment group (46.2 ± 12.4); control group (45.6 ± 12.4) • Sex (M/F): treatment group (11/9); control group (9/11) • Relevant comorbidities: not reported • Exclusion criteria: not reported
Interventions	Treatment group • Gabapentin (oral): 100 to 200 mg/day for 4 weeks Control group • Hydroxyzine (oral): 10 mg/day for 4 weeks
Outcomes	• Pruritus: mean VAS at baseline and after the intervention • Adverse effects
Notes	• Abstract-only publication • No reported conflict of interest • Correspondence: Dr Hamid Noshad, Assistant Professor of Nephrology, hamidnoshad1@yahoo.com • Translated from Farsi

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "...randomised in two groups..."
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "Double-blind", "Patients and investigators were not aware of the medications prescribed."

Noshad 2011 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	QUOTE: "Double-blind", "Patients and investigators were not aware of the medications prescribed."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled patients randomised and analysed at trial completion. No dropouts
Selective reporting (reporting bias)	Low risk	Mean and SE of VAS at baseline and after the intervention reported in full for both placebo and Gabapentin groups
Other bias	Unclear risk	Abstract-only publication; insufficient information to permit judgement

Omidian 2013

Study characteristics

Methods	• Study design: parallel RCT • Time frame: June to July 2011 • Duration of study/follow-up: 4 weeks
Participants	• Setting: single centre (inpatients) • Country: Iran • Inclusion criteria: aged 18 to 60 years; 3 time/week HD; minimum duration of pruritus 8 weeks • Number: treatment group (25); control group (25) • Mean age ± SD: 29.6 ± 12.7 years (groups not reported) • Sex (M/F): not reported • Relevant comorbidities: not reported • Exclusion criteria: known hypersensitivity to nicotinamide; suffering from other known skin diseases, liver disorders, metabolic disorders any other condition except for CKD causing pruritus; any serious systemic diseases; usage of antihistamines or other anti-pruritus drugs in the last 3 months; pregnant females and breast-feeding mothers
Interventions	Treatment group • Nicotinamide (oral): 500 mg twice/day for 4 weeks Control group • Placebo (oral): twice/day for 4 weeks
Outcomes	• Pruritus: mean VAS (5 cm) reported at baseline and weekly • Adverse effects
Notes	• No declared source of funding • Correspondence: Dr. Amir Feily, Skin and Stem Cell Research Center, Tehran University of Medical Sciences, Tehran, Iran E-mail: dr.feily@yahoo.com

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "Randomization was performed by using a simple random table"

Omidian 2013 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "The used medications were not revealed to the treating physicians."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	QUOTE: "The patients were oriented as to how to interpret their pruritus based on Visual Analogue Scale (VAS)"
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 dropout from Nicotinamide group
Selective reporting (reporting bias)	Low risk	All baseline and weekly results reported
Other bias	Low risk	No evidence of publication, funding, or other confounding bias

Ozaykan 2001

Study characteristics	
Methods	• Study design: cross-over RCT • Time frame: not reported • Duration of study/follow-up: 4 weeks treatment + 4 weeks washout
Participants	• Setting: single centre (inpatients) • Country: Turkey • Inclusion criteria: patients with ESKD on dialysis; minimum duration of pruritus 8 weeks • Number: 20 • Mean age ± SD (years): not reported • Sex (M/F): treatment group 1 (4/6); treatment group 2 (3/7) • Relevant comorbidities: not reported • Exclusion criteria: dermatological disease or systemic disease
Interventions	Treatment group 1 • Ondansetron (oral, tablet): 8 mg/day for 4 weeks Treatment group 2 • Cyproheptadine (oral, syrup): 8 mg/day for 4 weeks
Outcomes	• Pruritus: Duo score patient recorded every day
Notes	• No declared source of funding • No correspondence given

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Ozaykan 2001 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	QUOTE: "open, randomised and comparative study"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts in either group
Selective reporting (reporting bias)	Unclear risk	Baseline and weekly results all reported Group level data without individual patient level comparisons provided
Other bias	Low risk	No evidence of publication or funding bias

Pakfetrat 2014

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: August 2011 to June 2012 • Duration of study/follow-up: 6 weeks
Participants	• Setting: single centre (outpatients) • Country: Iran • Inclusion criteria: ESKD on HD; minimum duration of pruritus 6 weeks but did not respond to anti-pruritic drugs • Number: treatment group (50); control group (50) • Mean age ± SD (years): treatment group (55.6 ± 14.7); control group (51.0 ± 16.6) • Sex (M/F): treatment group (33/17); control group (27/22) • Relevant comorbidities: not reported • Exclusion criteria: dermatologic, liver, or metabolic diseases associated with pruritus; serum PTH > 300 pg/mL
Interventions	Treatment group • Turmeric (oral): 500 mg (22.1 curcumin), 3 times/day for 6 weeks Control group • Placebo (oral): 3 times/day for 6 weeks
Outcomes	• Pruritus: VAS and Duo score daily reported at baseline and at the end of treatment period
Notes	• No declared source of funding

Pakfetrat 2014 *(Continued)*

- Correspondence: L. Malekmakan, Department of Community Medicine, Shiraz Nephro-Urology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran; e-mail: malekl@sums.ac.ir

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "Factorial block randomisation was used for allocation sequence"
Allocation concealment (selection bias)	Low risk	QUOTE: "The allocation sequence was concealed from the researcher enrolling and assessing participants in sequentially numbered, opaque, sealed envelopes."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "Clinical investigators, laboratory personnel, and patients were all masked to the treatment assignment."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	QUOTE: "Clinical investigators, laboratory personnel, and patients were all masked to the treatment assignment."
Incomplete outcome data (attrition bias) All outcomes	Low risk	One dropout (1% attrition rate), unlikely to change study results
Selective reporting (reporting bias)	Low risk	All baseline and final results reported
Other bias	Low risk	No evidence for publication, funding, or other confounding bias

Pakfetrat 2018

Study characteristics

Methods	• Study design: parallel RCT • Time frame: March to September 2015 • Duration of follow-up: 8 weeks
Participants	• Setting: single centre (outpatients) • Country: Iran • Inclusion criteria: dialysed 3 times/week and complained of pruritus for more than 4 weeks • Number (randomised/analysed): treatment group (25/21); control group (25/21) • Mean age ± SD (years): treatment group (44.0 ± 15.5); control group (44.2 ± 17.1) • Sex (M/F): treatment group (18/7); control group (16/5) • Relevant comorbidities: not reported • Exclusion criteria: calcium X phosphorus > 55.0; P > 5.5, PTH > 300, selective serotonin reuptake inhibitors intolerance; liver disease; lupus patients who was on azathioprine and Cellcept; consumed emollients cream 2 weeks or antihistamine and gabapentin 1 month before study
Interventions	Treatment group • Sertraline (oral): 50 mg twice/day for 8 weeks

Pakfetrat 2018 *(Continued)*

	Control group • Placebo (oral): twice/day for 8 weeks
Outcomes	• Pruritus: VAS and Duo score daily reported at baseline and at the end of treatment period • SD for post intervention VAS and Duo scores missing however point estimates, baseline SDs, and P values reported
Notes	• The Vice-Chancellery of Research and Technology of Shiraz University of Medical Sciences financially supported this study • Correspondence: L. Malekmakan, Department of Community Medicine, Shiraz Nephro-Urology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran; e-mail: malekl@sums.ac.ir

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "...randomly we divided patients into two groups"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "This double blinded clinical trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	QUOTE: "This double blinded clinical trial"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	During the course of study one patient from control group died due to an accident and three patients of this group quit the study as a result of feeling no relief in their symptom. Twenty-one patients remained in control group
Selective reporting (reporting bias)	Low risk	Clearly reported
Other bias	Low risk	No evidence of publication, funding, or other confounding bias

Pauli-Magnus 2000

Study characteristics

Methods	• Study design: cross-over RCT • Time frame: not reported • Duration of study/follow-up: 4 weeks + 7 days washout + 4 weeks
Participants	• Setting: multicentre (4 sites) • Country: Germany • Inclusion criteria: aged 20 to 85 years; ESKD on HD or PD; minimum duration of pruritus 3 with sleep disturbances and activity interference • Number: 16 • Mean age ± SD (years): not reported

Pauli-Magnus 2000 *(Continued)*

	• Sex: not reported • Relevant comorbidities: not reported • Exclusion criteria: Kt/V > 1.2; no CKD-related pruritis; anaemia (Hb < 10 g/dL); taking opiates; taking steroids; dermatological disease; systemic disease
Interventions	Treatment group • Naltrexone (oral): 50 mg/day for 4 weeks Control group • Placebo (oral): daily for 4 weeks
Outcomes	• Pruritus: Duo score (will sleep) and VAS at 1,2, and 4 weeks of each study period • Change from week one to four in VAS
Notes	• "This work was supported by the Robert Bosch Foundation and the Khalil Foundation" • Correspondence to Dr. Christiane Pauli-Magnus, Department of Internal Medicine, Division of Nephrology, Robert-Bosch-Hospital, Auerbachstrasse 110, 70376 Stuttgart, Germany. Phone: 49 711 8101 3496 E-mail: thomas.mettang@rbk.de

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "randomised, double-blind, placebo-controlled crossover study"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "Double blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	QUOTE: "Double blind". Patient recorded their own scores "on a daily basis by marking a visual analogue scale (VAS)"
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 dropouts. Mostly from developing an indication for opiates. ITT protocol followed
Selective reporting (reporting bias)	Unclear risk	Means and CIs from each week reported for each of naltrexone and placebo Group level data without patient level comparisons provided. Correlation may inflate standard error. Carry-over effects unlikely due to washout periods
Other bias	Low risk	No evidence of publication or funding bias

Peck 1996

Study characteristics

Methods	• Study design: parallel RCT

Peck 1996 *(Continued)*

	• Time frame: enrolled from November 2002 to May 2003 • Duration of study/follow-up: 8 weeks
Participants	• Setting: multicentre (4 sites) (outpatients) • Country: USA • Inclusion criteria: ESKD on dialysis with pruritus • Number: treatment group 1 (8); treatment group 2 (9); treatment group 3 (8) • Mean age ± SD (years): treatment group 1 (54.8 ± 16.2); treatment group 2 (45.6 ± 17.4); treatment group 3 (29.5 ± 17.2) • Sex M/F: treatment group 1 (5/3); treatment group 2 (4/5); treatment group 3 (4/4) • Relevant comorbidities: not reported • Exclusion criteria: aged < 18 years and >78 years; DM; on beta blockers or L-carnitine; condition affecting fatty acid absorption and metabolism
Interventions	Treatment group 1 • Fish oil (oral): 1 g/capsule, 6 capsules/day for 8 weeks Treatment group 2 • Olive oil (oral): 1 g/capsule, 6 capsules/day for 8 weeks Treatment group 3 • Safflower oil (oral): 1 g/capsule, 6 capsules/day for 8 weeks
Outcomes	• Pruritus: mean modified Duo score at baseline and at the end of the treatment period • Adverse effects
Notes	• No declared source of funding • Correspondence to LW Peck, Dept of Foods and Nutrition, Purdue, University, 1264 Stone Hall, West Lafayette, IN 47906

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "Patients were randomly assigned into three groups"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "Double blinded"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double blinded, patient reported Duo score
Incomplete outcome data (attrition bias) All outcomes	High risk	16 dropouts out of 41 enrolled
Selective reporting (reporting bias)	Low risk	Detail table of results (mean, standard error) at baseline, postintervention, and net change for all groups

Peck 1996 *(Continued)*

Other bias	Low risk	No evidence of publication or funding bias

Pederson 1980

Study characteristics

Methods	• Study design: cross-over RCT • Time frame: not reported • Duration of study/follow-up: 16 weeks total (8 weeks treatment period each order unclear washout period)
Participants	• Setting: singe centre (outpatients) • Country: USA • Health status: ESKD on HD with pruritus • Number: 20 randomised; 9 deleted from the analysis • Mean age (range): 53 years (range 34 to 72) • Sex (M/F): 16/4 • Relevant comorbidities: not reported • Exclusion criteria: not reported
Interventions	Treatment group • Activated charcoal (oral): 6 g/day for 8 weeks Control group • Placebo (oral): daily for 8 weeks
Outcomes	• Pruritis: 6 point scale at baseline and at endpoint
Notes	• No declared source of funding • Correspondence: James A. Pederson M.D. Veterans Administration Medical Center, 921 N.E. 13th Street Oklahoma City

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "Patients were randomly assigned..."
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double blinded, "treatments "administered orally in identical opaque capsules", "iron pills masked the charcoal stained stools"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double blind", unclear is assessors blinded
Incomplete outcome data (attrition bias)	High risk	Likely 9 dropouts/20, patients dropped for low compliance

Pederson 1980 *(Continued)*
All outcomes

Selective reporting (reporting bias)	High risk	Incomplete results with arbitrary markers for improvement
Other bias	Unclear risk	No washout indicated, unlike other naltrexone studies; no evidence of publication or funding bias

Peer 1996

Study characteristics

Methods	• Study design: cross-over RCT • Time frame: not reported • Duration of study/follow-up: 7 days + 7 days washout + 7 days
Participants	• Setting: single centre (inpatients) • Country: Israel • Inclusion criteria: ESKD on dialysis with severe persistent pruritus • Number: treatment first group (8); control first group (7) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: non-renal pruritus causes
Interventions	Treatment group • Naltrexone (oral): 50 mg/day for 7 days Control group • Placebo (oral): daily for 7 days
Outcomes	• Pruritus: VAS every 6 hours reported as mean VAS at baseline and end of treatment periods
Notes	• "The study was supported by Travenol Laboratories, Israel. Naltrexone was given by Du Pont Pharmaceutical, USA" • Correspondence: Prof Adran Iaina Dept of Nephrology, Ichilov Hospital, Tel Aviv Medical Centre • Additional data provided by Dr Peer

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "entered a randomised double-blind placebo controlled crossover study (figure 1)"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "Double blind"

Peer 1996 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double blind. Patient recorded their own scores
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled patients completed the trial and were analysed
Selective reporting (reporting bias)	Unclear risk	Unclear reporting of placebo itch score SDs Group level data without patient level comparisons provided. Correlation may inflate standard error. Carry-over effects unlikely due to washout periods.
Other bias	Low risk	No evidence of publication or funding bias

Pour-Reza-Gholi 2007

Study characteristics	
Methods	• Study design: cross-over RCT • Time frame: not reported • Duration of study/follow-up: 7 days + 7 days washout + 7 days
Participants	• Setting: single centre (inpatients) • Country: Iran • Health status: ESKD on dialysis with pruritus • Number: 24 • Mean age ± SD: 48.0 ± 5.6 years • Sex (M/F): 13/11 • Relevant comorbidities: not reported • Exclusion criteria: Kt/V < 1.2; hypercalcaemia > 11.5 mg/dL; hyperphosphataemia > 6.5 mg/dL; hypo to hyperparathyroidism; hypoalbuminaemia; hypermagnesaemia; no CKD-related pruritis; anaemia (Hb < 10 g/dL)
Interventions	Treatment group • Doxepin (oral): 10 mg twice/day for 1 week Control group • Placebo (oral): twice/day for 1 week
Outcomes	• Pruritus: complete, relative, and no improvement reported at the end of the treatment periods for each patient • Adverse effects
Notes	• No declared conflict of interest • Correspondence: Fatemeh Pour-Reza-Gholi, MD, Department of Nephrology, Shaheed Labbafinejad Medical Center, 9th Boustan, Pasdaran, Tehran, Iran Tel: +98 21 2256 7222 E-mail: pourrezagholi@unrc.ir

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Pour-Reza-Gholi 2007 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	QUOTE: "They were randomly assigned..."
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "...placed in another capsule in order to provide placebo capsules similar in shape, size, and colour." "The patients and the physicians involving in their management were blind to the randomization."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	QUOTE: "The patients and the physicians involving in their management were blind to the randomization. Assessments based on clinician subjective reports."
Incomplete outcome data (attrition bias) All outcomes	Low risk	One patient dropout from doxepin group; did not complete placebo portion
Selective reporting (reporting bias)	Unclear risk	Aggregate results reported, arbitrary and subjective reporting of outcomes Group level data without patient level comparisons provided. Correlation may inflate standard error. Carry-over effects unlikely due to washout periods.
Other bias	Low risk	No evidence of publication, funding, or other confounding bias

Rad 2017

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: December 2014 to March 2015 • Duration of study/follow-up: 12 weeks
Participants	• Setting: multicentre (3 sites) (outpatients) • Country: Iran • Inclusion criteria: aged 18 and 65 years; not blind or deaf; ESKD after completing 3 months HD; KT/V of 1; AV fistulas; undergone HD 3 times/week, with each session lasting 4 hours; history of pruritus during HD for the last 2 months • Number: treatment group (30); control group (30) • Mean age ± SD (years): treatment group (53.1 ± 10.0); control group (55.8 ± 8.4) • Sex (M/F): treatment group (17/13); control group (15/15) • Relevant comorbidities: not reported • Exclusion criteria: psychological or severe mood and emotional disorders; endocrine disorders; pregnancy; skin disorders; pneumonia; acute complications during HD (ataxia syndrome, embolism, dysrhythmia, cardiopulmonary, high blood pressure, arrest, or coma); pruritic skin changes during the dialysis sessions; introduction to transplant during the study; intolerance to cold dialysis
Interventions	Treatment group • Cool dialysate: 35.5ºC, 3 times/week for 1 week Control group • Normal dialysate: 37ºC, 3 time/week for 1 week

Rad 2017 *(Continued)*

Outcomes	• Pruritus: VAS (10 cm) with correlated data regression model that was fitted with generalised estimating equations
Notes	• No declared conflicts of interest • Elahe Jaghouri, School of Nursing and Midwifery, Sabzevar University of Medical Sciences, Sabzevar, IR Iran. Tel: +98-5134446070, E-mail: jaghorie1@mums.ac.ir

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "The random permuted block method was used"
Allocation concealment (selection bias)	Low risk	QUOTE: "the [researcher] was unaware of whether they were assigned to the intervention or control", "triple blinded"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	QUOTE: "triple blinded"; unclear how one can blind patients to temperature
Blinding of outcome assessment (detection bias) All outcomes	Low risk	QUOTE: "triple blinded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No post randomisation dropouts
Selective reporting (reporting bias)	High risk	Only baseline VAS reported. Quantitative results of the regression not reported
Other bias	Unclear risk	No evidence of publication or funding bias

Rivory 1984

Study characteristics

Methods	• Study design: crossover RCT • Time frame: 20 days • Duration of study/follow-up: 20 days
Participants	• Setting: multicentre (3 sites) (outpatients) • Country: France • Inclusion criteria: chronic HD patients for > 1 year, suffering from pruritus evolving for more than a month • Number: 13 • Mean age ± SD (years): not reported • Sex (M/F):7/6 • Relevant comorbidities: not reported • Exclusion criteria: not reported
Interventions	Treatment group

Rivory 1984 *(Continued)*

	• Nicergoline (oral): 30 mg/day • Nicergoline 5 mg as a continuous IV infusion Control group • Oral and IV placebo
Outcomes	• VAS
Notes	• Funding not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE " in a random order"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE "in double blind manner"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	QUOTE "in double blind manner"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts reported
Selective reporting (reporting bias)	High risk	Only nonspecific, interpreted results reported
Other bias	Unclear risk	Abstract only publication

Shariati 2010

Study characteristics

Methods	• Study design: cross-over RCT • Time frame: not reported • Duration of study/follow-up: 2 weeks + 2 days washout + 2 weeks
Participants	• Setting: single centre (outpatients) • Country: Iran • Inclusion criteria: on HD with pruritis • Number: treatment group (15); treatment group 2 (15) • Mean age: 52.2 years • Sex: not reported • Relevant comorbidities: not reported

Shariati 2010 *(Continued)*

	• Exclusion criteria: other diseases which may cause pruritus, dermatological disease.
Interventions	Treatment group 1 • Charcoal (oral): 6 g capsule, 3 times/day for 2 weeks treatment group 2 • Aluminium hydroxide (oral): 30 mL syrup, 3 times/day for 2 weeks
Outcomes	• Pruritus: VAS and measurement of pruritus scale (MPS)
Notes	• In Arabic

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation table
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "Blinded" while discussing participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	QUOTE: "Blinded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% dropouts
Selective reporting (reporting bias)	Low risk	Full results reported with paired testing
Other bias	Low risk	No evidence of publication, funding, or other confounding bias

Sherjeena 2017

Study characteristics

Methods	• Study design: parallel RCT • Time frame: April 2012 to March 2013 • Duration of study/follow-up: 12 weeks
Participants	• Setting: single centre (outpatients) • Country: India • Inclusion criteria: aged > 18 years; ESKD on HD with pruritus score > 5 on the VAS • Number: treatment group (15); control group (15) • Median age range: treatment group (46 to 55 years); control group (56 to 65 years) • Sex (M/F): overall ratio 2:1

Sherjeena 2017 *(Continued)*

	• Relevant comorbidities: identical rates ESKD aetiology: DM (13), hypertension (5), drug-induced (1) • Exclusion criteria: history of photosensitivity; early kidney disease (Stage I, II and III); pregnancy; breastfeeding; pruritus secondary to other skin or systemic diseases
Interventions	Treatment group • UVB (whole body): 200 to 1038 mJ/cm^2 every 3rd day for 15 sessions Control group • Cetirizine (oral): 10 mg/day for the same duration • Liquid paraffin (topical)
Outcomes	• Pruritus: patient completed mean VAS weekly for 4 weeks then at 3 and 6 months
Notes	• Study letter • No declared conflict of interest • Correspondence: Pentamveli Beegum Sherjeena, Melethil House, Karinchapadi, Vattaloor P.O., Malappuram - 676 507, Kerala, India

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	QUOTE: "By alternation"
Allocation concealment (selection bias)	High risk	QUOTE: "By alternation"
Blinding of participants and personnel (performance bias) All outcomes	High risk	QUOTE: "Unblinded"
Blinding of outcome assessment (detection bias) All outcomes	High risk	QUOTE: "Unblinded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Low risk	Results reported in full
Other bias	Low risk	No evidence of publication or funding bias

Shirazian 2013

Study characteristics

Methods	• Study design: parallel RCT • Time frame: May 2010 to August 2011 • Duration of study/follow-up: 12 weeks

Shirazian 2013 *(Continued)*

Participants	• Setting: single centre • Country: USA • Inclusion criteria: ESKD on HD > 18 years; excessive described pruritis • Number: treatment group (25); control group (25) • Mean age ± SD (years): treatment group (66.1 ± 14.7); control group (66.2 ± 13.7) • Sex M/F: treatment group (15/10); control group (14/11) • Relevant comorbidities: not reported • Exclusion criteria: PTH < 70 pg/mL or > 1000 pg/mL; serum phosphorus > 7.0 mg/dL; serum calcium > 11 mg/dL; active malignancy or current ergocalciferol treatment
Interventions	Treatment group • Ergocalciferol (oral): 50,000 IU once/week for 12 weeks Control group • Placebo (oral): once/week for 12 weeks
Outcomes	• Pruritis: patient-completed mean VAS and baseline and every 2 weeks • Mean reduction displayed graphically and SD reported separately.
Notes	• Support: "This study was supported by a research grant from the Council of Renal Nutrition of the National Kidney Foundation." • Financial Disclosure: The authors declare that they have no relevant financial Correspondence: Shayan Shirazian, MD, 200 Old Country Road, Suite 135, Mineola, NY 11501. E-mail: sshirazian@winthrop.org

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "Computer-generated random numbers"
Allocation concealment (selection bias)	Low risk	QUOTE: "A research pharmacist prepackaged ergocalciferol and placebo tablets into opaque bottles. A research nurse, who did not participate in con sent, pruritus surveys, or study analysis assigned patients to the appropriate pill bottle. The research nurse also dispensed the medication to the patient (within 1 week of the prerandomization visit and randomisation assignment)."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "Patients and investigators were blinded to the allocation of the study drug."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	QUOTE: "Patients and investigators were blinded to the allocation of the study drug."
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT protocol, 6 dropout (4 in Ergocalciferol group)
Selective reporting (reporting bias)	Low risk	Baseline and result fully reported at www.clinicaltrial.gov
Other bias	Low risk	No evidence of publication or funding bias

Silva 1994

Study characteristics	
Methods	• Study design: cross-over RCT • Time frame: not reported • Duration of study/follow-up: 7 days + 7 days washout + 7 days
Participants	• Setting: single centre (inpatients) • Country: Brazil • Inclusion criteria: "Pruritus"; ESKD on HD • Number: treatment first group (14); control first group (15) • Mean age ± SD (years): treatment first group (57.5 ± 7.3); control group (50.5 ± 11.2) • Sex (M/F): treatment first group first (12/2); control first group (5/10) • Relevant comorbidities: not reported • Exclusion criteria: "Fertile" women; non-CKD pruritus
Interventions	Treatment group • Thalidomide (oral): 100 mg/day for 1 week Control group • Placebo (oral): daily for 1 week
Outcomes	• Pruritus: 0 to 3 record 3 times/day. Final score defined as percent of maximum score possible • Responder defined as final score reduction >50%. Responder rates reported at end of treatment periods
Notes	• No declared conflict of interest • Correspondence: Jocemir Ronaldo Lugon MD, PhD, R.S. Luiz Gonzaga 851 20910-061 Rio de Janeiro, Brazil

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "were randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "double blind"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	18/29 completed the study after randomisation, no ITT

Silva 1994 *(Continued)*

Selective reporting (reporting bias)	High risk	Only subjective responder rates recorded with arbitrary cut offs. Group level data without patient level comparisons provided. Carry-over effects unlikely due to washout periods.
Other bias	Low risk	No evidence for publication or funding bias

Silverberg 1977

Study characteristics

Methods	• Study design: parallel RCT • Time frame: not reported • Duration of study/follow-up: 7 weeks (3 week baseline recording and 4 week treatment period)
Participants	• Setting: single centre (inpatients) • Country: Israel • Inclusion criteria: "Longstanding pruritis" on HD • Number: treatment group (5); control group (5) • Mean age ± SD (years): not reported • Sex: all males • Relevant comorbidities: not reported • Exclusion criteria: not reported
Interventions	Treatment group • Cholestyramine (oral): 5 mg twice/day for 4 weeks Control group • Placebo (oral): twice/day for 4 weeks
Outcomes	• Pruritus: 0 to 3 recording 3 times a day. Mean reporting at end of 3 week baseline and 4 week treatment period for each individual patient recorded • Adverse effects
Notes	• No declared conflict of interest • Correspondence: DS Silverberg MD University of Tel Aviv, Dept of Nephrology, Sheba Medical Centre, Tel Hashomer, Israel

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "patients were randomly assigned to two treatments"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "Double blinded"

Silverberg 1977 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled patient completed the trial and were analysed
Selective reporting (reporting bias)	Low risk	All patient outcomes reported
Other bias	Low risk	No evidence of publication, funding, or other confounding bias

Sja'bani 1997

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: not reported • Duration of study/follow-up: 5 weeks
Participants	• Setting: single centre (inpatients) • Country: Indonesia • Inclusion criteria: aged 18 to 65 years on HD with pruritis • Number: treatment group (15); control group (14) • Mean age ± SD (years): treatment group (52.3 ± 14.7); control group (46.3 ± 9.0) • Sex: not reported • Relevant comorbidities: "No significant difference in sex, age, weight, height, or blood pressure" • Exclusion criteria: non-HD-related skin or allergic pathology
Interventions	Treatment group • rHuEPO (SC): 2000 UI, twice/day for 4 weeks Control group • Placebo (oral): twice/day for 4 weeks
Outcomes	• Pruritus score: mean VAS score at end of treatment period
Notes	• Abstract-only publications • No declared conflict of interest • Correspondence: Gadjah Mada University, Yogyakarta, Indonesia

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	QUOTE: "randomised double blind study design"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

Sja'bani 1997 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "Double blind"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	5 dropout (2 placebo, 1 rHuEPO) reasons not reported
Selective reporting (reporting bias)	Unclear risk	Baseline VAS scores not reported
Other bias	Unclear risk	Insufficient information to permit judgement

Solak 2012

Study characteristics	
Methods	• Study design: cross-over RCT • Time frame: not reported • Duration of study/follow-up: 14 week (2 x 6 week treatment period and 2 week washout)
Participants	• Setting: single centre (outpatient) • Country: Turkey • Health status: ESKD on dialysis • Inclusion criteria: aged > 18 years; prior diagnosis of peripheral neuropathy or being on drug treatment for peripheral neuropathy for at least 3 months; minimum 40 mm pain score in the Short Form of McGill Pain Questionnaire, undergoing HD for at least 6 months; achievement of dialysis adequacy (Kt/V > 1.2) • Number (randomised/analysed): 50/40 • Mean age ± SD: 58.2 ± 13.7 years • Sex M/F: 12/28 • Relevant comorbidities: not reported "No significant difference in sex, age, weight height, blood pressure" • Exclusion criteria: presence of hepatic, cardiopulmonary and uncontrolled psychiatric disease; pain syndromes other than peripheral neuropathy; specific dermatologic disease, which may cause pain and/or pruritus; abnormal blood counts (WBC < 2500/mm^3 and platelet count < 10,000/ mm^3; presence of active malignancy; untreated hypothyroidism; patients with extremity amputation
Interventions	Treatment group 1 • Gabapentin (oral): 300 mg once/day for 6 weeks Treatment group 2 • Pregabalin (oral): 75 mg once/day for 6 weeks
Outcomes	• Mean change in VAS score from start to end of or each treatment period • Adverse effects only reports "no statistical difference"
Notes	• No declared conflicts of interest

Solak 2012 *(Continued)*

- Correspondence: Dr Yalcin Solak, Konya Universitesi, Meram Tip Fakultesi, Hemodiyaliz Sekreterligi, Meram, Konya, Turkey. Email: yalcinsolakmd@gmail.com

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "Patients were randomised into either gabapentin (25 patients) or pregabalin (25 patients) treatment arms using computer generated random numbers."
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	5 dropouts from each group. ITT unclear
Selective reporting (reporting bias)	Unclear risk	Change (mean and SD) in VAS clearly reported for each treatment type and period Group level data without patient level comparisons provided. Carry-over effects unlikely due to washout periods.
Other bias	Low risk	No evidence of publication or funding bias

Spencer 2015

Study characteristics

Methods	• Study design: parallel RCT • Time frame: not reported • Duration of study/follow-up: 15 days
Participants	• Setting: multicentre (number of sites not reported) • Country: USA • Inclusion criteria: HD patients with persistent moderate-to-severe daily pruritus for 6 weeks prior • Number: treatment group (33); control group (32) • Mean age ± SD (years): treatment group (60 ± 12); control group (60.1 ± 16) • Sex (M/F): treatment group (16/17); control group (15/17) • Relevant comorbidities: not reported • Exclusion criteria: not reported
Interventions	Treatment group • CR845 (IV): 1 µg/kg every dialysis session for 15 days

Spencer 2015 *(Continued)*

	Control group • Placebo (IV): every dialysis session for 15 days
Outcomes	• Change in itch from baseline to Days 12 to 15 using VAS
Notes	• Additional data obtained from poster presented at the ASN Kidney Week 2015 Annual Meeting; November 5-8, 2015; San Diego, CA • Fully supported by Cara Therapeutics, Inc. The authors received medical writing assistance from Edward Weselcouch, PhD, of PharmaWrite (Princeton, NJ), which was funded by Cara Therapeutics, Inc. RHS, JWS, and FM are employees of Cara Therapeutics, Inc. • Correspondence: Frédérique Menzaghi, PhD fmenzaghi@caratherapeutics.com

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "Multi-center (21 US sites), randomised (1:1), double-blind, placebo-controlled, parallel-group Phase 2 study"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "double-blind, placebo-controlled, parallel-group Phase 2 study"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	QUOTE: "double-blind, placebo-controlled, parallel-group Phase 2 study"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	One dropout in the placebo group, unlikely to affect outcomes
Selective reporting (reporting bias)	Low risk	Mean and SD of changes and baseline VAS score reported for both CR845 and placebo
Other bias	High risk	The present study was fully supported by Cara Therapeutics, Inc. The authors received medical writing assistance from Edward Weselcouch, PhD, of PharmaWrite (Princeton, NJ), which was funded by Cara Therapeutics, Inc. RHS, JWS, and FM are employees of Cara Therapeutics, Inc

Spencer 2017

Study characteristics

Methods	• Study design: Crossover RCT • Time frame: not reported • Duration of study/follow-up: 8 weeks
Participants	• Setting: multicentre (number of sites not reported) • Country: USA • Inclusion criteria: HD patients with moderate-to-severe pruritus

Spencer 2017 *(Continued)*

- Number: treatment group 1 (44); treatment group 2 (41); treatment group 3 (44); control group (45)
- Mean age ± SD (years): "Demographics and baseline features were well balanced across treatment groups"
- Sex M/F: "Demographics and baseline features were well balanced across treatment groups"
- Relevant comorbidities: "Demographics and baseline features were well balanced across treatment groups"
- Exclusion criteria: not reported

Interventions	Treatment group 1 • CR845 (IV): 0.5 µg/kg with dialysis for 8 weeks Treatment group 2 • CR845 (IV): 1.0 µg/kg with dialysis for 8 weeks Treatment group 3 • CR845 (IV): 1.5 µg/kg with dialysis for 8 weeks Control group • Placebo (IV): with dialysis for 8 weeks
Outcomes	• Itch: 5-D itch scale, mean change in VAS score from start to end of or each treatment period
Notes	• Abstract-only publications • No declared conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "Patients were randomised"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts not reported
Selective reporting (reporting bias)	High risk	1.0 µg/kg and placebo results not fully reported
Other bias	High risk	Abstract-only publications; funded by Cara Therapeutics

Subach 2001

Study characteristics	
Methods	• Study design: three-way cross-over RCT • Time frame: not reported • Duration of study/follow-up: not reported
Participants	• Setting: not reported • Country: USA • Inclusion criteria: HD related itch • Number: 23 patients • Mean age ± SD (years): not reported • Sex M/F: not reported • Relevant comorbidities: not reported • Exclusion criteria: not reported
Interventions	• Quote: "23 patient with HDI were to receive 3 doses of ondansetron 8mg, diphenhydramine 25mg, or matching placebo during 9 separate occasions of HDI"
Outcomes	• VAS 10 cm at 30, 60, and 120 min after administration • Itch relief defined as 50% reduction in baseline. 3-way ANOVA used for analysis
Notes	• Abstract-only publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "in a randomised..."
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "double blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	QUOTE: "double-blind"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts not reported
Selective reporting (reporting bias)	Unclear risk	Unclear reporting. Assumed to be results from 120 min, but not clear. No results of the ANOVA reported
Other bias	Unclear risk	Abstract only; no declaration relating to conflicts of interest

Suwanpidokkul 2007

Study characteristics	
Methods	• Study design: cross-over RCT • Time frame: 10 weeks • Duration of study/follow-up: 10 weeks
Participants	• Setting: not reported • Country: Thailand • Inclusion criteria: HD patients with pruritus (VAS > 50 mm) • Number: 19 patients (subgroups not reported) • Mean age: 56.9 years • Sex M/F: not reported • Relevant comorbidities: not reported • Exclusion criteria: not reported
Interventions	Treatment group 1 • Gabapentin first: 100 mg/day for 4 weeks, washout 2 weeks, then loratadine 10 mg/day for 4 weeks Treatment group 2 • Loratadine first: 10 mg/day for 4 weeks, washout 2 weeks, then gabapentin 100 mg/day for 4 weeks Route not specified but implied oral
Outcomes	• Itch: VAS, difference in mean change between treatment groups • Adverse effects: occur during treatment of either Loratadine or Gabapentin
Notes	• Abstract-only publications • Additional data obtained from poster presentation presented at Kidney Week 2017; New Orleans, LA; Oct 31 – Nov 5 • Funded by Cara Therapeutics

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "Patients were randomised assigned"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "double-blinded"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	QUOTE: "double-blinded"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Partial reporting on 5 dropout

Suwanpidokkul 2007 *(Continued)*

Selective reporting (reporting bias)	Low risk	Within and between group changes clearly reported
Other bias	Low risk	Abstract only; no declaration relating conflicts of interest

Tamimi 1999

Study characteristics

Methods	• Study design: parallel RCT • Time frame: 6 months • Duration of study/follow-up: 6 months
Participants	• Setting: ambulatory setting • Country: UK • Inclusion criteria: HD and PD patients with intractable itch • Number (randomised/analysed): 33/16 (numbers per group not reported) • Mean age ± SD (years): not reported • Sex M/F: not reported • Relevant comorbidities: not reported • Exclusion criteria: not reported
Interventions	Treatment group • Gamma-linolenic acid (evening primrose oil) (emulsion): 10 mL (32 mg/mL) twice/day Control group • Placebo
Outcomes	• Severity of itch • Response to treatment • Kidney and liver function
Notes	• Letter to journal • Funding: "Evening primrose oil and placebo were supplied by Scotia Pharmaceuticals Ltd."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information to permit judgement

Tamimi 1999 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	High risk	17/33 patients failed to complete study
Selective reporting (reporting bias)	High risk	No data available to meta-analyse
Other bias	Unclear risk	Insufficient information to permit judgement

Tan 1990

Study characteristics

Methods	• Study design: cross-over RCT • Time frame: not reported • Duration of study/follow-up: 21 days (2 x 1 week treatment periods and 7 days washout)
Participants	• Setting: multicentre (5 sites) • Country: Singapore • Inclusion criteria: pruritis and aged > 16 years on HD with pruritus • Number: 30 • Mean age ± SD: 41.8 ± 11.2 years • Sex (M/F): 24/6 • Relevant comorbidities: not reported • Exclusion criteria: allergy to camphor, menthol, phenol or crotamiton; intercurrent skin conditions; use of any other topical skin preparation for 3 days prior to the commencement of the study
Interventions	Treatment group 1 • Sarna lotion (topical): 0.5% each of camphor, menthol, and phenol "as required" for 7 days Treatment group 2 • Eurax cream (topical): 10% crotamiton "as required" for 7 days
Outcomes	• VAS at baseline at 4 hour and 7 days post baseline for each treatment period
Notes	• Stiefel Laboratories "for the generous provision of the study medications." • Otherwise no reported conflict of interest • Correspondence: Dr Chorh-Chuan Tan, Nuffield Department of Medicine, Level 5, John Radcliffe Hospital, Headington, Oxford OX3 9DU, UK

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "The order of study medicaments used was randomly assigned for consecutive patients according to a computer-generated randomization code."
Allocation concealment (selection bias)	Low risk	QUOTE: "Both observer and patient were blinded to the identity of the medications, which were contained in identical opaque plastic bottles."

Tan 1990 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "Both observer and patient were blinded to the identity of the medications, which were contained in identical opaque plastic bottles."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	QUOTE: "Both observer and patient were blinded to the identity of the medications, which were contained in identical opaque plastic bottles."
Incomplete outcome data (attrition bias) All outcomes	Low risk	One dropout, unlikely to change results
Selective reporting (reporting bias)	Unclear risk	Baseline and final scores recorded in full Group level data without patient level comparisons provided. Carry-over effects unlikely due to washout periods
Other bias	Low risk	Interventions used "as required". No evidence of publication or funding bias

Tapia 1977

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: not reported • Duration of study/follow-up: 1 week
Participants	• Setting: single centre (inpatients) • Country: USA • Inclusion criteria: pruritis during HD, aged 16 to 65 years • Number: treatment group (10); control group (10) • Mean age: 39 years • Sex (M/F): 13/7 • Relevant comorbidities: not reported • Exclusion criteria: not reported
Interventions	Treatment group • Lidocaine (IV): 200 mg infused over 15 min during HD and additional 3 times if no effect Control group • Placebo (IV): infused over 15 min during HD and additional 3 times if no effect
Outcomes	• Itch relief or no relief (binary) after treatment vs baseline itch status (all patients reporting itch). Unclear definition of relief • Adverse effects
Notes	• Supported by NIH grant • No reported conflict of interest • Correspondence: Dr Tapia Rogosin Kidney Center, New York Hospital-Cornell Medical Center, 525 E 68th St New York, NY 10021

Tapia 1977 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "Table of random numbers"
Allocation concealment (selection bias)	Low risk	QUOTE: "Vial arranged in order and patient enters study area with unlabelled vials"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "Double Blind", "Identical vials"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	QUOTE: "investigator unaware of vial order"
Incomplete outcome data (attrition bias) All outcomes	High risk	Four placebo patients unaccounted for in analysis
Selective reporting (reporting bias)	High risk	Simple binary response fully reported, only 6 placebo patients reported on with no explanation
Other bias	Low risk	No evidence of publication or funding bias

Tarng 1996

Study characteristics

Methods	• Study design: cross-over RCT • Time frame: not reported • Duration of study/follow-up: 8 weeks (no washout)
Participants	• Setting: single centre (outpatients) • Country: Taiwan • Inclusion criteria: aged 27 to 85 years; ESKD on HD; moderate to severe pruritis • Number: 14 • Mean age: 52.7 years • Sex (M/F): 13/6 • Relevant comorbidities: not reported • Exclusion criteria: non-moisturiser topical agents used in the past 2 weeks
Interventions	Treatment group • Capsaicin cream (topical): 0.025% cream 4 times/day for 8 weeks Control group • Placebo (topical): 4 times/day for 8 weeks
Outcomes	• Severity of pruritus: 4-point scale at baseline and then weekly to treatment completion

Tarng 1996 *(Continued)*

Notes	• No declared conflicts of interest • Correspondence: Der-Cherng Tarng, MD, Division of Nephrology, Veterans General Hospital-Taipei, No 201, Sec 2 Shih-Pai Road, Taipei. 11217, Taiwan

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "Treatment order is block-randomized with the use of computer-generated random numbers"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "Double blinded"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double blind, doctor evaluated, complex assignments
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2 dropouts, not ITT
Selective reporting (reporting bias)	High risk	Placebo results not reported Group level data without patient level comparisons provided
Other bias	Low risk	No evidence of publication or funding bias

Taylor 1983

Study characteristics

Methods	• Study design: parallel RCT • Time frame: not reported • Duration of study/follow-up: 6 weeks
Participants	• Setting: single centre (outpatients) • Country: Ireland • Inclusion criteria: ESKD on HD; no other aetiology of pruritus • Number: treatment group (6); control group (5) • Mean age ± SD (years): treatment group (49.0 ± 6.1); control group (50.4 ± 5.3) • Sex (M/F): not reported • Relevant comorbidities: not reported • Exclusion criteria: kidney transplantation; severe illness
Interventions	Treatment group • UV-A (exposure): 40 min exposure (10, 180 cm 85W UV-A lamps) 3 times/week for 6 weeks Control group

Taylor 1983 *(Continued)*

	• Placebo (exposure): 40 min exposure 3 times/week for 6 weeks
Outcomes	• Pruritus: VAS
Notes	• No declared conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "randomised into control and treatment groups"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unblinded (used a radiation barrier)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded (used a radiation barrier)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	High risk	Qualitative results only
Other bias	Low risk	No evidence of publication or funding bias

Tol 2010

Study characteristics

Methods	• Study design: cross-over RCT • Time frame: not reported • Duration of study/follow-up: 9 weeks (2 x 4 week treatment periods, 1 week washout
Participants	• Setting: single centre (inpatients) • Country: Slovakia • Inclusion criteria: CKD-related pruritis for at least 8 weeks • Number: 14 • Mean age ± SD: 59.7 ± 17.2 years • Sex 9M/F): 7/7 • Relevant comorbidities: not reported • Exclusion criteria: aged < 18 years; concomitant dermatological, liver, or metabolic diseases; pregnant or lactating women
Interventions	Treatment group • Gabapentin (oral): 300 mg every HD session for 4 weeks

Tol 2010 *(Continued)*

	Control group • Placebo (oral): every HD session for 4 weeks
Outcomes	• Mean VAS • Post-sleep Inventory • Mental scale • Depression scale at baseline and end of treatment periods
Notes	• No declared conflicts of interest • Correspondence: Dr Huseyin Atalay Tel: 0332-223 72 06; Email: hatalay1971@yahoo.com

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "On a random basis..."
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "Blinded"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Patient recorded VAS independent of assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient enrolled completed the trial
Selective reporting (reporting bias)	High risk	Placebo results not reported Intervention level data without patient level comparisons provided. Carry-over effects unlikely due to washout periods
Other bias	Low risk	No evidence of publication or funding bias

TREVITR02 2017

Study characteristics

Methods	• Study design: parallel RCT • Time frame: June 2014 to March 2015 • Duration of study/follow-up: 4 weeks
Participants	• Setting: multicentre (number of sites not reported) (inpatients) • Country: USA • Inclusion criteria: HD for ≥ 3 months with a mean of the 6 numerical rating scale scores during the week prior to randomisation > 4.5 on an 11-point scale • Number: treatment group 1 (128); treatment group 2 (120); control group (125)

TREVITR02 2017 *(Continued)*

- Mean age ± SD (years): treatment group 1 (55 ± 12); treatment group 2 (55 ± 12); control group (57 ± 13)
- Sex (M): treatment group 1 (58%); treatment group 2 (54%); control group (59%)
- Relevant comorbidities
  - DM: treatment group 1 (50%); treatment group 2 (56%); control group (48%)
- Exclusion criteria: not reported

Interventions	Treatment group 1 • Nalbuphine ER (oral): 60 mg twice/day (force titrated reaching dose after the first week) for 8 weeks Treatment group 3 • Nalbuphine ER (oral): 120 mg twice/day (force titrated reaching dose after the second week) for 8 weeks Control group • Placebo (oral): twice/day for 8 weeks
Outcomes	• Mean duration of pruritus: change in numerical rating scale scores
Notes	• Funded and conducted by Trevi Pharmaceuticals • Primary contact: Thomas Sciascia, MD

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "Randomization was performed by site personnel, using a centralized interactive web-based randomization system, which assigned unique blister card numbers reflecting the blinded treatment assignment"
Allocation concealment (selection bias)	Low risk	QUOTE: "Randomization was performed by site personnel, using a centralized interactive web-based randomization system, which assigned unique blister card numbers reflecting the blinded treatment assignment"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "The sponsor, study site personnel, and all contract research organization personnel involved in the conduct of the trial were blinded to treatment assignment. Matching placebo was used"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	QUOTE: "The sponsor, study site personnel, and all contract research organization personnel involved in the conduct of the trial were blinded to treatment assignment. Matching placebo was used"
Incomplete outcome data (attrition bias) All outcomes	High risk	Not ITT, high number of post-randomisation dropout with explanation
Selective reporting (reporting bias)	Low risk	Numerical rate scale clearly reported
Other bias	High risk	For-profit pharmaceutical development

van Leusen 1978

Study characteristics	
Methods	• Study design: cross-over RCT • Time frame: not reported • Duration of study/follow-up: 4 weeks (unknown washout period)
Participants	• Setting: single centre (inpatients) • Country: Netherlands • Inclusion criteria: ESKD on HD • Number: 10 • Mean age ± SD (years): not reported • Sex: not reported • Relevant comorbidities: not reported • Exclusion criteria: not reported
Interventions	Treatment group • Cholestyramine (oral): 5 mg twice/day for 4 weeks Control group • Placebo (oral methylcellulose): twice/day for 4 weeks
Outcomes	• Pruritus: 4 point itch severity scale before and after both interventions for each individual patient recorded
Notes	• Correspondence: Municipal Hospital, Arnhem Netherlands

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	QUOTE: "randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	QUOTE: "double-blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Low risk	Results clearly reported
Other bias	Unclear risk	Washout period unclear; no evidence of publication or funding bias

Vessal 2010

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: August 2008 to June 2009 • Duration of study/follow-up: 8 weeks + 4 weeks follow-up
Participants	• Setting: multicentre (2 sites) (inpatients) • Country: Iran • Health status: aged > 18 years with ESKD on HD; pruritus for > 6 weeks • Number (randomised/analysed): treatment group (32/21); control group (30/19) • Mean age ± SD (years): treatment group (56.90 ± 15.49); control group (57.47 ± 13.6) • Sex (M/F): treatment group (12/9); control group (8/11) • Relevant comorbidities: not reported • Exclusion criteria: any dermatologic, liver, or metabolic diseases associated with pruritus
Interventions	Treatment group • Cromolyn (oral): 135 mg 3 times/day for 8 weeks Control group • Placebo (oral): 3 times/day for 8 weeks
Outcomes	• Patient recorded VAS 2 to 3 times a day. Mean VAS reported at baseline at after each treatment period
Notes	• No declared conflicts of interest • Correspondence: Ghazal Vessal; E-mail: gvessal@yahoo.com

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	QUOTE: "Stratified randomization method where the prognostic factor was the gender variable"
Allocation concealment (selection bias)	Low risk	QUOTE: "Drug packages were prepared by the principal investigator (G.V.). Both the participants and the investigator that administered the interventions and assessed the outcomes were blinded to group assignment. Code breaking was performed at the end of data analysis."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "Drug packages were prepared by the principal investigator (G.V.). Both the participants and the investigator that administered the interventions and assessed the outcomes were blinded to group assignment. Code breaking was performed at the end of data analysis."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	QUOTE: "Drug packages were prepared by the principal investigator (G.V.). Both the participants and the investigator that administered the interventions and assessed the outcomes were blinded to group assignment. Code breaking was performed at the end of data analysis."
Incomplete outcome data (attrition bias) All outcomes	High risk	11 dropouts from each arm. Not analysed on ITT • Cromolyn: 2 died, 3 transferred, 5 non-compliant, 1 transplanted • Placebo: 1 died, 2 transferred, 5 non-compliant, 3 adverse events

Vessal 2010 *(Continued)*

Selective reporting (reporting bias)	Low risk	Clearly reported full results
Other bias	Low risk	No evidence of publication or funding bias.

Wikstrom 2005

Study characteristics

Methods	• Study design: parallel RCT (study 1); crossover RCT (study 2) • Time frame: not reported • Duration of study/follow-up: 1 run-in week + 4 week
Participants	• Setting: multicentre (number of sites not reported) • Country: Japan • Inclusion criteria: severe, uncontrolled pruritus caused only by ESKD; > 18 years; undergoing routine HD • Number: study 1 treatment group (26); study 1 control group (25); study 2 treatment group (16); study 2 control group (18) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Relevant comorbidities: not reported • Exclusion criteria: pregnant, nursing, or wanting to become pregnant; patients whose pruritus occurred only during dialysis; and patients who had participated in a clinical trial or received an experimental drug within 30 d of trial start; history of drug/alcohol abuse, allergy to opioids or other drug allergies, or a psychiatric disorder
Interventions	Study 1 treatment group • Nalfurafine (IV): 5 µg, 3 times/week immediately after completion of each HD for 4 weeks Study 1 control group • Placebo (IV): 3 times/week immediately after completion of each HD for 4 weeks Study 2 • 1 week run-in + 2 week + 3 week washout + 1 week run-in + 2 week
Outcomes	• Patient recorded mean VAS every 12 hours reported at baseline at after each treatment period • Mean VAS • Adverse effects limited in details and no analysis
Notes	• No declared conflicts of interest • Correspondence: Dr. Yuji Ueno, Clinical Development Center, Toray Industries Inc., 8-1, Mihama 1-chome, Urayasu, Chiba 279-8555, Japan. Phone: +81-47-350-6754; E-mail: yuji_ueno@nts.toray.co.jp

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "patients were randomly assigned in this study"

Wikstrom 2005 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "Double blinded"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double blinded, Patient recorded VAS independent of assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% attrition and balanced, analysed with ITT
Selective reporting (reporting bias)	Low risk	Cross-over period 2 ignored, but mentioned in protocol
Other bias	Low risk	No evidence of publication, funding, or other confounding bias

Yoshimoto-Furuie 1999

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: not reported • Duration of study/follow-up: 6 weeks
Participants	• Setting: single centre • Country: Japan • Health status: ESKD on HD with pruritus • Number: treatment group (9); control group (7) • Mean age ± SD (years): treatment group (58 ± 19); control group (46 ± 16) • Sex M/F: treatment group (2/7); control group (4/3) • Relevant comorbidities: not reported • Exclusion criteria: Kt/V < 1.2
Interventions	Treatment group • Evening primrose oil (oral): 2 capsules/day (containing 360 mg of linoleic acid, 50 mg oleic acid and 45 mg of gamma-linoleic acid) for 6 weeks Control group • Linoleic acid (oral): 2 x 500 mg capsules/day for 6 weeks
Outcomes	• Pruritus: mean 5-point scale at baseline and post intervention
Notes	• No declared conflict of interest • Correspondence: Hirotoshi Echizen, MD, PhD, Dept of Pharmacotherapy, Meiji Pharmaceutical University 2-522-1 Noshio, Kiyose
Risk of bias	

Yoshimoto-Furuie 1999 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "The patients were randomly assigned into two study groups:"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "in a double-blind manner."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient enrolled completed the trial
Selective reporting (reporting bias)	Unclear risk	No actual itch scores reported. Only bar graph and P-values
Other bias	Low risk	No evidence of publication, funding, or other confounding bias

Young 2009

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: not reported • Duration of study/follow-up: 4 weeks
Participants	• Setting: single centre (outpatients) • Country: USA • Inclusion criteria: aged 18 to 70 years on HD with at least two episodes of itch over a period of 2 weeks, each lasting for 2 minutes or more; and symptoms of itch in a regular pattern over 6 months • Number: treatment group (14); control group (14) • Mean age: 53.5 years • Sex M/F: 7/7 • Exclusion criteria: no other active disease that could explain the itch
Interventions	Treatment group • Pramoxine (topical): 1% twice/day for 4 weeks Control group • Placebo (topical): twice/day for 4 weeks
Outcomes	• Pruritus: mean VAS at baseline and post intervention; only regression results reported • Adverse effects

Young 2009 *(Continued)*

Notes	• Dr Fleischer has the following potential conflicts covering the past 5 years: * Advisory board – Amgen, Astellas, Galderma, Stiefel * Consultant – Astellas, Combe, Galderma, Gerson Lehrman, Intendis, Kikaku America International, Merz * Investigator – 3M, Abbott, Amgen, biogen, Dow, Coria, Galderma, gSK, Genentech, Healthpoint, Intendis, Medicis, Novartis, Ortho-Neutrogena, Pfizer, Steifel; * Speaker bureau – Amgen, Astellas, Connetics, Coria, Ferndale, Galderma, Intendis, Medicis, Novartis * Stockholder – None • Funding obtained from Stiefel Laboratories. • Correspondence: Alan B. Fleischer jr, Department of Dermatology, Wake Forest University School of medicine, medical Center boulevard, Winston Salem, NC 27157, USA. Fax: 1 336 716 7732. e-mail: afleisch@wfubmc.edu

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "a randomised, double-blind, controlled comparative trial"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "a randomised, double-blind, controlled comparative trial"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Clinical evaluation, double blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	One dropout (~3%), unlikely to changes study results
Selective reporting (reporting bias)	High risk	Only a regression slope result reported
Other bias	High risk	Financial conflicts of interest - Funding obtained from Stiefel Laboratories (GSK), a manufacturer of skin care products

Yue 2015

Study characteristics

Methods	• Study design: parallel RCT • Time frame: not reported • Duration of study/follow-up: 12 weeks
Participants	• Setting: single centre (outpatients) • Country: China

Yue 2015 *(Continued)*

- Inclusion criteria: aged ≥ 16 years; undergoing stable HD for at least 3 months; suffering from persistent pruritus
- Number (randomised/analysed): treatment group 1 (67/64); treatment group 2 (64/60); control group (57/57)
- Mean age ± SD (years): treatment group 1 (57.7 ± 16.9); treatment group 2 (56.5 ± 12.7); control group (57.2 ± 10.8)
- Sex (M): treatment group 1 (62.9%); treatment group 2 (60%); control group (57.9%)
- Relevant comorbidities
  - DM: treatment group 1 (12.9%); treatment group 2 (11.7%); control group (12.5%)
- Exclusion criteria: hepatic or cardiopulmonary disease; uncontrolled psychiatric disease; specific dermatologic disease or metabolic disease that may cause pruritus; diabetic neuropathy; history of drug allergy

Interventions	Treatment group 1 • Pregabalin (oral): 75 mg twice/week for 12 weeks Treatment group 2 • Ondansetron (oral): 8 mg/day for 12 weeks Control group • Placebo (oral): once/day for 12 weeks
Outcomes	• Mean VAS, Duo score, Pittsburgh Sleep quality Index, SF-12 * Assessed and reported and 0, 2, 4, 6, 8, and 12 weeks • Some adverse effects reported but not analysed
Notes	• No reported conflicts of interest • J. Meng Blood Purification Center, General Hospital of Jinan Military Area Command, Jinan, Shandong, People's Republic of China e-mail: drmjz90@163.com

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "Patients were randomly assigned to 12 weeks of treatment"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	QUOTE: "Double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	QUOTE: "prescription of pregabalin for UP was not mentioned in the dispensatory."
Incomplete outcome data (attrition bias) All outcomes	Low risk	~5% dropout rate. Unclear in following ITT
Selective reporting (reporting bias)	Low risk	Baseline and final itch results reported in full for all interventions and placebo (mean and standard error)

Yue 2015 *(Continued)*

Other bias	Low risk	No evidence of publication, funding, or other confounding bias

Zhang 2016a

Study characteristics

Methods	• Study design: parallel RCT • Time frame: October 2013 to February 2014 • Duration of study/follow-up: 12 weeks
Participants	• Setting: single centre (outpatients) • Country: China • Inclusion criteria: on stable HD for at least six months with pruritus • Number: treatment group 1 (20); treatment group 2 (20) • Mean age ± SD (years): treatment group 1 (66 ± 16); treatment group 2 (59 ± 18) • Sex (M): treatment group 1 (75%); treatment group 2 (75%) • Relevant comorbidities: not reported • Exclusion criteria: biliary atresia; liver problems; cancer; metabolic disorders; other diseases related to systemic pruritus
Interventions	Treatment group 1 • Haemoperfusion + HD: haemoperfusion cartridge attached to high flux dialyzer (Polyflux 14 L, Gambro) followed by regular dialysis; every 4 weeks for 12 weeks Treatment group 2 • Haemoperfusion + HDF: haemoperfusion cartridge connected to the arterial end of a German Fresenius 4008S HD machine with an AV600 polysulfone filter and a haemofilter, every 4 weeks for 12 weeks
Outcomes	• Pruritus: VAS
Notes	• Not declared conflicts of interest • Dr. Changying Xing, Department of Nephrology, The First Affiliated Hospital of Nanjing Medical University, Jiangsu Province Hospital, 300 Guangzhou Road, Nanjing 210029, Jiangsu Province, P. R. of China. Tel: 0086-25-6813- 6462; Fax: 0086-25-6813-6462; E-mail: cyxing1962@163.com

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	QUOTE: "randomised"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias)	High risk	Open-label study

Zhang 2016a *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts post randomisation
Selective reporting (reporting bias)	Low risk	VAS clearly reported for both groups
Other bias	Low risk	No evidence of publication or funding bias

APD - automated peritoneal dialysis; BP - blood pressure; CKD - chronic kidney disease; DM - diabetes mellitus; (rHu)EPO - (recombinant human) erythropoietin; ESKD - end-stage kidney disease; Hb - haemoglobin; HCT - haematocrit; HD - haemodialysis; HDF - haemodiafiltration; ITT - intention-to-treat; IV - intravenous; Kt/V - dialysis adequacy; M/F - male/female; PD - peritoneal dialysis; (i)PTH - (intact) parathyroid hormone; RCT - randomised controlled trial; SBP - systolic blood pressure; SC - subcutaneous; SD - standard deviation; SE - standard error; SLE - systemic lupus erythematosus; UV - ultraviolet; VAS - visual analogue scale; WBC - white blood cell/s

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bousquet 1989	QUOTE: "All patients with pruritus entered in a crossover, double-blind trial with nicergoline. In a first period of six dialyses, they received either nicergoline (daily oral dose, 30 mg, and intravenous dose during dialyses, 5 mg) or placebo. In the second period of six dialyses, patients received the crossover treatment" COMMENT: Randomisation unclear; unable to confirm
Burrai 2014	Wrong intervention: not applicable pruritus intervention for this review (music)
Cavalcanti 2003	Wrong intervention: not applicable pruritus intervention for this review (homeopathy)
Che-Yi 2005	Wrong intervention: not applicable pruritus intervention for this review (acupuncture)
CTRI/2016/04/006870	Wrong intervention: not applicable pruritus intervention for this review (self care)
CYCLE-HD 2016	Wrong intervention: not applicable pruritus intervention for this review (exercise for cardiovascular health)
Gao 2002	Wrong intervention: not applicable pruritus intervention for this review (acupuncture)
Ghura 1998	Wrong study design: no control
IRCT201303093560N2	Wrong intervention: not applicable pruritus intervention for this review (massage)
IRCT2015091010076N6	Wrong intervention: not applicable pruritus intervention for this review (massage)
Jedras 2003	Wrong intervention: not applicable pruritus intervention for this review (acupuncture)
Joffe 1985	Other: study terminated due to lack of enrolment
Kilic Akca 2016	Wrong intervention: not pruritus intervention (acupuncture)
Legat 2017	Wrong population: includes all pruritus, not just uraemic pruritus

Study	Reason for exclusion
Little 1995	QUOTE: " At entry patients were selected to receive loratidine or placebo for two weeks after which crossover occurred" COMMENT: Randomisation unclear and no mention of dose
Lücker 1986	Protocol only. No update in > 30 years
Marquez 2012	We did not consider allocation based on dialysis schedule as quasi-randomisation. More than alternation or other forms of quasi-RCT this introduces additional bias
NCT00577967	Recruitment status unknown (not yet recruiting as of 7 July 2007)
NCT00793156	Recruitment status unknown (not yet recruiting as of 4 February 2010)
NCT01073501	Recruitment status unknown (not yet recruiting as of 23 February 2010)
NCT01620580	Recruitment status unknown (not yet recruiting as of 4 February 2010)
NCT01660243	Recruitment status: terminated due to insufficient patient recruitment (17 March 2016)
NCT01852318	Recruitment status unknown (not yet recruiting as of 15 April 2014)
NCT02032537	Recruitment status unknown (not yet recruiting as of 10 January 2014)
NCT02432508	Wrong intervention: not applicable pruritus intervention for this review (acupuncture)
Och 2000	Wrong intervention: not applicable pruritus intervention for this review (acupressure)
Rehman 2018	Wrong intervention: not applicable pruritus intervention for this review (acupressure)
Ro 2002	Wrong intervention: not applicable pruritus intervention for this review (aromatherapy)
Rui 2002	Wrong intervention: not applicable pruritus intervention for this review (acupuncture)
Sanchez 1986	Wrong control: UVA versus PUVA are indistinguishable interventions
Wang 2014e	We did not consider allocation based on dialysis schedule as quasi-randomisation. More than alternation or other forms of quasi-RCT this introduces additional bias
Weisshaar 2003	Areas on each patient are randomised to treatment rather than patients
Yan 2015	Wrong intervention: not applicable pruritus intervention for this review (acupressure)
Yoshida 2017	We did not consider allocation based on dialysis schedule as quasi-randomisation. More than alternation or other forms of quasi-RCT this introduces additional bias
Zadeh 2015	Wrong intervention: not applicable pruritus intervention for this review (massage)
Zhang 2011d	Wrong intervention: not applicable pruritus intervention for this review (acupuncture)

Characteristics of studies awaiting classification *[ordered by study ID]*

Bai 2002

Methods	• Parallel RCT
Participants	• HD patients (80)
Interventions	Treatment group • Chinese herb-based cream: twice/day for 2 weeks Control group • Lotion with no active ingredients: twice/day for 2 weeks
Outcomes	• Improvement: 5-point VAS
Notes	• Study reported in systematic review by Simonsen 2017 • Waiting to obtain full-text

NCT01513161

Methods	• Multi-centre, double blinded, placebo-controlled, parallel, fixed dose, phase III RCT
Participants	• Setting: multicentre • Country: South Korea • Adults aged > 20 years Inclusion criteria • CKD patients who regularly receive HD 3 times/week and are not likely to have a serious treatment change or acute symptoms during the study period • Patients for whom all the conventional pruritus treatments in section (2) are not enough • Patients whose VAS scores are measured both after breakfast and dinner for 5 days or more of the last 7 days of the predose observation period and whose mean of whichever the higher VAS scores after breakfast or dinner is ≥ 50 mm • Patients with whichever was the higher VAS score after breakfast or dinner for the last 7 days during the preliminary observation day (measured VAS score if one is missing) is more than ≥ 20 mm for 5 days or more • Patients who are judged to have pruritus both during the day and at night for more than two days based on the Shiratori's severity criteria assessed by the subject at days of fifth and sixth HD and the day of HD after the completion of the predose observation period, and whose whichever the higher pruritis score measured during the day or at night is 3 (moderate) for two days or more Exclusion criteria • Malignant tumour; depression, schizophrenia or dementia as complications; currently have Child-pugh class B or C hepatic cirrhosis as complications; clinically significant hepatic or cardiovascular diseases which cannot be controlled by diet or drug therapy; life-threatening arrhythmia; unstable angina or myocardial infarction within 6 months; PCI or CABG within 6 months; NYHA class III or IV congestive heart failure; atopic dermatitis or chronic urticaria as complications; allergic to opioid drugs; dependence on drug or alcohol; received phototherapy for pruritus within one month before signing the consent form; participated in the study of TRK-820 and received the study drug or who were already enrolled in this study; participated in other clinical studies (including the ones using artificial kidney and medical equipment), and received the study drug or treatment with clinical equipment within one month before signing the consent form; pregnant women, lactating women and patients of childbearing potential who do not use contraceptive methods; cannot report VAS scores by their own for any reason at the principal investigator or study personnel's discretion; complications or history can impact the results of this study at the

NCT01513161 *(Continued)*

	principal investigator or sub-investigator's discretion; not proper to participate in this study at the principal investigator or study personnel's discretion
Interventions	Treatment group 1 • Nalfurafine hydrochloride (TRK-820): soft capsule containing 2.5 µg nalfurafine hydrochloride. Start with 2.5 µg of oral administration once daily and can be increased up to 5 µg if necessary Treatment group 2 • Nalfurafine hydrochloride (TRK-820): soft capsule containing 2.5 µg nalfurafine hydrochloride. Start with 2.5 µg of oral administration once daily, and can be increased up to 5 µg if necessary. Control group • Placebo (oral)
Outcomes	• Change in pruritus degree measured by VAS score at 4 weeks (2 weeks measurement with only conventional treatment + 2 weeks measurement with conventional treatment & investigational products) • Changes in Shiratori's severity scores assessed by the subject at 4 weeks (2 weeks measurement with only conventional treatment + 2 weeks measurement with conventional treatment & investigational products)
Notes	• Suhng Gwon Kim, MD, PhD • Sponsors and Collaborators: SK Chemicals Co., Ltd; Toray Industries, Inc • No results published (May 2020)

NCT02696499

Methods	• Double blind, placebo-controlled, parallel-arm, multicentre, phase 2, proof-of-concept efficacy and safety RCT
Participants	• Setting: multicentre • Country: USA • Adults aged 18 to 80 years Inclusion criteria • Diagnosis of ESKD requiring HD for at least 3 months prior to the screening period • Receiving conventional HD (i.e., not haemofiltration or haemodiafiltration) • Pruritus present for at least 6 weeks of screening • Mean pruritus severity score on a NRS > 4 • Patient-Assessed Disease Severity Scale Type B or C at screening • Documentation of a URR > 65% or single-pooled Kt/V > 1.4 during screening • Willing and able to provide written informed consent Exclusion criteria • Current or recent history of clinically significant medical condition, laboratory abnormality, or illness that could put the patient at risk or compromise the quality of the study data as determined by the investigator; myocardial infarction within 6 months or unstable angina, acute coronary syndrome, or interventional coronary procedure within 2 months of screening; upper or lower respiratory tract infection (including sinus infection) within 4 weeks of screening; severely symptomatic cardiopulmonary disease defined by the use of home oxygen treatment, dyspnoea at rest or with minimal exertion, uncontrolled arrhythmias (e.g. atrial fibrillation with inadequate rate control), or history of life-threatening arrhythmias (e.g. cardiac arrest or syncope related to arrhythmia); acute exacerbation of asthma or chronic obstructive pulmonary disease resulting in hospi-

NCT02696499 *(Continued)*

	talisation or visit to an emergency department or urgent care clinic within 6 months of screening; hospitalisation for any medical reason other than for a pre-planned procedure or dialysis access related procedure within the 2 weeks of screening; malignancy requiring active treatment with a systemic drug; participation in any other investigation drug study within 4 weeks of screening; current or anticipated use of baclofen, gabapentin, pregabalin and nalbuphine for the treatment of pruritus; current or anticipated use of glucocorticoids administered intravenously, orally, or transdermally; pregnant or breastfeeding females, or if of child-bearing potential unwilling to practice acceptable means of birth control or abstinence during the study
Interventions	Treatment group • PA101B: 40 mg administered via inhalation twice daily for 7 weeks Control group • Placebo: administered via inhalation twice daily for 7 weeks
Outcomes	• Itching intensity at 7 weeks (NRS) • Pruritus-specific QoL at 7 weeks (Skindex-10) • Pruritus-specific sleep quality at 7 weeks (Itch MOS) • Assessment of depression at 7 weeks (Beck Depression Inventory-II) • PGIC at 7 weeks
Notes	• Sponsors and Collaborators: Patara Pharma • No results published (May 2020)

NCT02747979

Methods	Parallel, open-label, RCT
Participants	Inclusion criteria: • Willingness to sign an informed consent • Stable HD treatment for more than 3 months, undergoing 2 to 3 times HD a week for 4 to 5 hours/session • middle or large molecules retention defined as immunoreactive parathyroid hormone > 400 pg/mL, beta-2 microglobulin > 5000 pg/mL, CRP > 10 mg/L • Refractory pruritus, carpal tunnel syndrome, restless leg syndrome, hyperparathyroidism, or other refractory complications Exclusion criteria: • Incapable or reluctant to sign the informed consent or comply the schedule • platelet count < 60 x 10^9/L or disturbance in coagulation, tendency of severe bleeding or acute bleeding • Severe hypotension and heart or lung insufficiency • Known hypersensitive or contradiction or intolerance to dialyzer or adsorbents • Attend to other clinic trial now or in recent 30 days
Interventions	• HD only • HD plus haemoperfusion (HA330) • HD plus haemoperfusion (HA130)
Outcomes	• Longitudinal changes in itching • Longitudinal changes of serum beta-2 microglobulin • Longitudinal changes of serum iPTH

NCT02747979 *(Continued)*

	• Longitudinal changes of CRP • Longitudinal changes of serum ADMA • Longitudinal changes of serum BMP2 • Longitudinal changes of the nutritional status evaluated using the serum level of albumin, the subjective global assessment score and BMI
Notes	• Actual study completion date: May 2010 • Last verified April 2016 • No results published • Xue Qing Yu, Sun Yat-sen University

ADAMA - asymmetric dimethylarginine; BMI - body mass index; BMP2 - bone morphogenetic protein 2; CABG - coronary artery bypass grafting; CKD - chronic kidney disease; CRP - C-reactive protein; ESKD - end-stage kidney disease; HD - haemodialysis; MOS - medical outcomes study; NRS - numerical rating scale; NYHA - New York Heart Association; PCI - percutaneous coronary intervention; PGIC - Patient Global Impression of Change; (i)PTH - (intact) parathyroid hormone; QoL - quality of life; RCT - randomised control trial; URR - urea reduction ratio; VAS - visual analogue scale

Characteristics of ongoing studies *[ordered by study ID]*

ACTRN12614000677606

Study name	In patients with end stage renal failure on dialysis, does evening primrose oil, compared to omega-3 fish oil and placebo improve pruritis?
Methods	Double blinded, placebo controlled RCT
Participants	Patients with ESKD undergoing dialysis (in hospital or at home)
Interventions	• Evening primrose oil supplementation • Omega -3 fish oil
Outcomes	VAS, rule of nines and questions involving QoL
Starting date	Not yet recruiting
Contact information	Dr Jane Holt Department of Renal Medicine Wollongong Hospital Dudley Street Wollongong NSW 2500 + 61 02 4222 5443
Notes	

DON'T ITCH 2015

Study name	A phase IV, randomised, double-blind, controlled, parallel group trial to evaluate the effectiveness and safety of balneum plus vs emollient in the treatment of uraemic pruritus in haemodialysis patients
Methods	Double-blind, controlled, parallel RCT
Participants	Receiving HD for the treatment of ESKD for at least 3 months; aged > 18 years
Interventions	• E45 cream • Emollient
Outcomes	The primary outcome measure will be reduction in itch intensity as measured by VAS
Starting date	13 November 2015
Contact information	Jacqueline Nevols Queen Alexandra Hospital Portsmouth PO6 3LY UK 02392286000 jacqueline.nevols@porthosp.nhs.uk
Notes	

IRCT201311152417N14

Study name	Effect of omega-3 on pruritus scale in hemodialysis patients
Methods	Double-blinded, parallel RCT
Participants	HD for at least 3 months; pruritus duration > 8 weeks; without any dermatologic problems; no hypersensitivity to omega-3; no malabsorption or other gastrointestinal problems (chronic diarrhoea > 2 weeks); not using anticoagulant and antiplatelet drugs Exclusion criteria: non-compliance; kidney transplantation; antihistamine or gabapentin using; anaemia (Hb < 7 g/dL); PTH > 300 µg/L; phosphorus >7 mg/dL; INR rising; aged > 16 years
Interventions	Omega-3 fatty acid supplementation
Outcomes	Questionnaire (VAS)
Starting date	22 November 2013
Contact information	Firouzeh Moeinzadeh University of Medical Sciences Iran, Islamic Republic of +98 31 1625 5555

IRCT201311152417N14 *(Continued)*

	addressmoinzade@resident.mui.ac.ir
Notes	

IRCT2015051411940N3

Study name	The effect of aloe vera gel on pruritus severity of hemodialysis patients
Methods	Double-blind, controlled, parallel RCT
Participants	Receiving HD for the treatment of ESKD for at least 3 months; aged > 18 years
Interventions	Aloe vera gel will be used 2 times in a day for 1 month
Outcomes	5-D pruritus scale
Starting date	23 July 2015
Contact information	Azam Malek Hoseini Arak University of Medical Sciences, Alamolhoda St, Arak Arak 3817834467 Iran +98 86 3226 7892 malekhoseni.aram@gmail.com
Notes	

NCT03422653

Study name	A multicenter, double-blind, randomised, placebo-controlled study to evaluate the safety and efficacy of intravenous CR845 in hemodialysis patients with moderate-to-severe pruritus, with a 52-week open label extension
Methods	Double-blind, parallel RCT
Participants	Receiving HD for the treatment of ESKD for at least 3 months; aged > 18 years
Interventions	IV CR845 0.5 µg/kg administered after each dialysis session (3 times/week) versus IV placebo
Outcomes	Reduction in itch intensity Improvement in itch-related QoL
Starting date	20 February 2018
Contact information	Frédérique Menzaghi, PhD, Cara Therapeutics
Notes	

NCT03636269

Study name	A multicenter, double-blind, randomised, placebo-controlled study to evaluate the safety and efficacy of intravenous CR845 in hemodialysis patients with moderate-to-severe pruritus, with a 52-week open label extension
Methods	Parallel, double blind, RCT
Participants	350
Interventions	CR845 0.5 µg/kg versus placebo
Outcomes	24-hour worst itching intensity (NRS)
Starting date	17 July 17 2018
Contact information	Georgine Ragsdale, PharmD 203-406-3700 clinicaltrials.gov@caratherapeutics.com
Notes	

SNUG 2019

Study name	Safety and efficacy of PG102P for the coNtrol of prUritus in patients underGoing hemodialysis (SNUG Trial): study protocol for a randomised control trial
Methods	Parallel, double blind, RCT
Participants	80
Interventions	PG102P 1.5 g/day
Outcomes	VAS
Starting date	May 1, 2018
Contact information	Yong Chul Kim, MD +82-2-2072-1724 imyongkim@gmail.com Seoul National University Boramae Medical Center
Notes	

ESKD - end-stage kidney disease; Hb - haemoglobin; HD - haemodialysis; INR - international normalised ratio; NRS - numerical rating scale; PTH - parathyroid hormone; QoL - quality of life; RCT - randomised controlled trial; VAS - visual analogue scale

DATA AND ANALYSES

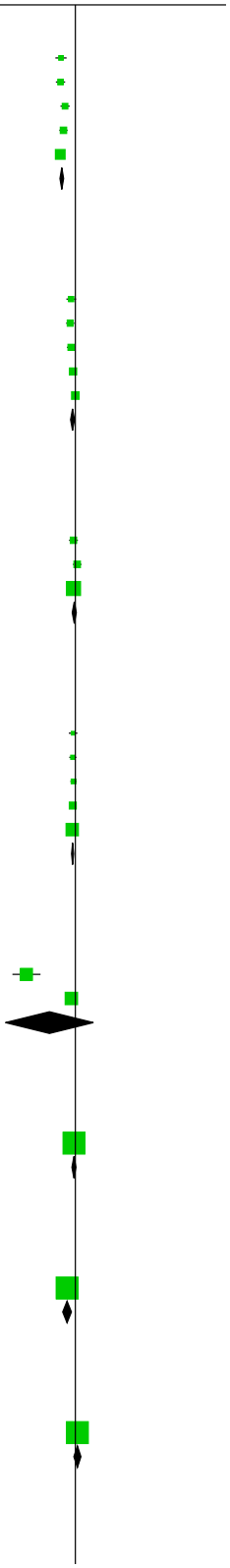
Comparison 1. Pharmacological interventions (oral or IV)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Itch	30		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1.1 GABA analogues	5	297	Std. Mean Difference (IV, Random, 95% CI)	-2.14 [-2.43, -1.85]
1.1.2 GABA analogues versus antihistamine	5	220	Std. Mean Difference (IV, Random, 95% CI)	-0.44 [-0.75, -0.14]
1.1.3 Ondansetron	3	183	Std. Mean Difference (IV, Random, 95% CI)	-0.17 [-0.49, 0.15]
1.1.4 Kappa-opioid agonist	4	661	Std. Mean Difference (IV, Random, 95% CI)	-0.43 [-0.60, -0.27]
1.1.5 Mu-opioid antagonist	2	62	Std. Mean Difference (IV, Random, 95% CI)	-4.10 [-11.05, 2.85]
1.1.6 Nalbuphine	1	179	Std. Mean Difference (IV, Random, 95% CI)	-0.22 [-0.54, 0.10]
1.1.7 Cromolyn	1	40	Std. Mean Difference (IV, Random, 95% CI)	-1.31 [-2.00, -0.62]
1.1.8 Nicotinamide	1	50	Std. Mean Difference (IV, Random, 95% CI)	0.32 [-0.23, 0.88]
1.1.9 EPO	1	20	Std. Mean Difference (IV, Random, 95% CI)	-0.50 [-1.39, 0.39]
1.1.10 Cholestyramine	2	20	Std. Mean Difference (IV, Random, 95% CI)	0.00 [-0.89, 0.89]
1.1.11 Montelukast	2	87	Std. Mean Difference (IV, Random, 95% CI)	-1.40 [-1.87, -0.92]
1.1.12 Sertraline	1	46	Std. Mean Difference (IV, Random, 95% CI)	-0.56 [-1.15, 0.03]
1.1.13 Lidocaine	1	16	Std. Mean Difference (IV, Random, 95% CI)	-0.81 [-1.87, 0.25]
1.1.14 Gabapentin versus pregabalin	1	40	Std. Mean Difference (IV, Random, 95% CI)	0.01 [-0.61, 0.63]
1.1.15 GABA analogues versus doxepin	1	72	Std. Mean Difference (IV, Random, 95% CI)	-0.84 [-1.33, -0.36]
1.2 Itch (dichotomous)	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.2.1 Lidocaine	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.2.2 Thalidomide	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2.3 Doxepin	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

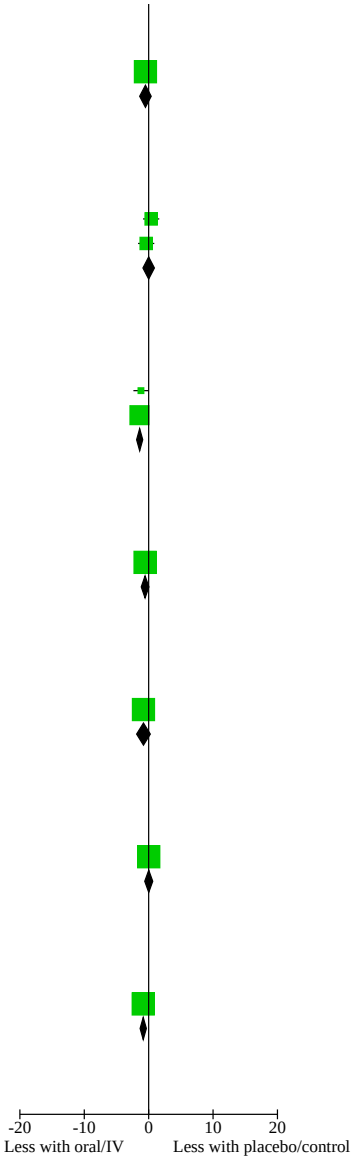
Analysis 1.1. Comparison 1: Pharmacological interventions (oral or IV), Outcome 1: Itch

Study or Subgroup	Oral/IV Mean	SD	Total	Placebo/control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 GABA analogues								
Naini 2007	-6.7	2.6	17	-1.5	1.8	17	10.8%	-2.27 [-3.15 , -1.39]
Gunal 2004	-6.6	2	25	-0.8	2.8	25	15.7%	-2.35 [-3.08 , -1.61]
Naghibi 2007	-5.4	2.4	20	-0.8	3.1	20	16.0%	-1.63 [-2.35 , -0.90]
Nofal 2016	-5.82	2.89	27	-0.1	3.11	27	20.0%	-1.88 [-2.53 , -1.23]
Yue 2015	-6.6	2.2	62	-2	1.55	57	37.5%	-2.38 [-2.86 , -1.91]
Subtotal (95% CI)			**151**			**146**	**100.0%**	**-2.14 [-2.43 , -1.85]**
Heterogeneity: Tau² = 0.00; Chi² = 3.97, df = 4 (P = 0.41); I² = 0%								
Test for overall effect: Z = 14.48 (P < 0.00001)								
1.1.2 GABA analogues versus antihistamine								
Suwanpidokkul 2007	-3.9	1.8	14	-2.07	3.4	14	13.8%	-0.65 [-1.42 , 0.11]
Noshad 2011	-6	5.5	20	-0.3	8.1	20	18.1%	-0.81 [-1.45 , -0.16]
Marin 2013	-0.66	0.47	20	-0.33	0.47	20	18.4%	-0.69 [-1.33 , -0.05]
Amirkhanlou 2016	-0.89	0.42	26	-0.76	0.31	26	23.4%	-0.35 [-0.89 , 0.20]
Gobo-Oliveira 2018	-4	2.6	30	-4	2.3	30	26.3%	0.00 [-0.51 , 0.51]
Subtotal (95% CI)			**110**			**110**	**100.0%**	**-0.44 [-0.75 , -0.14]**
Heterogeneity: Tau² = 0.03; Chi² = 5.12, df = 4 (P = 0.28); I² = 22%								
Test for overall effect: Z = 2.83 (P = 0.005)								
1.1.3 Ondansetron								
Ashmore 2000	-1.4	4.98	16	-0.1	3.38	16	19.7%	-0.30 [-1.00 , 0.40]
Murphy 2003	-0.9	2.69	17	-1.7	2.76	17	20.8%	0.29 [-0.39 , 0.96]
Yue 2015	-2.5	1.9	60	-2	1.55	57	59.5%	-0.29 [-0.65 , 0.08]
Subtotal (95% CI)			**93**			**90**	**100.0%**	**-0.17 [-0.49 , 0.15]**
Heterogeneity: Tau² = 0.01; Chi² = 2.26, df = 2 (P = 0.32); I² = 12%								
Test for overall effect: Z = 1.03 (P = 0.31)								
1.1.4 Kappa-opioid agonist								
Wikstrom 2005 (1)	-2.18	2.32	16	-1.35	2.29	18	5.9%	-0.35 [-1.03 , 0.33]
Wikstrom 2005 (2)	-2.5	3.17	26	-1.27	2.83	25	8.8%	-0.40 [-0.96 , 0.15]
Spencer 2015	-3.31	4.87	33	-1.9	4.81	32	11.3%	-0.29 [-0.78 , 0.20]
Spencer 2017	-3.2	1.07	45	-1.9	3.63	129	23.1%	-0.41 [-0.75 , -0.07]
Kumagai 2010	-2.25	1.939	226	-1.3	1.885	111	51.0%	-0.49 [-0.72 , -0.26]
Subtotal (95% CI)			**346**			**315**	**100.0%**	**-0.43 [-0.60 , -0.27]**
Heterogeneity: Tau² = 0.00; Chi² = 0.69, df = 4 (P = 0.95); I² = 0%								
Test for overall effect: Z = 5.17 (P < 0.00001)								
1.1.5 Mu-opioid antagonist								
Peer 1996	-8.3	0.8314	15	-1	1	15	48.9%	-7.72 [-9.94 , -5.51]
Pauli-Magnus 2000	-2.92	2	16	-1.69	1.8	16	51.1%	-0.63 [-1.34 , 0.08]
Subtotal (95% CI)			**31**			**31**	**100.0%**	**-4.10 [-11.05 , 2.85]**
Heterogeneity: Tau² = 24.46; Chi² = 35.69, df = 1 (P < 0.00001); I² = 97%								
Test for overall effect: Z = 1.16 (P = 0.25)								
1.1.6 Nalbuphine								
TREVITR02 2017	-3.95	3.6	124	-3.2	2.7	55	100.0%	-0.22 [-0.54 , 0.10]
Subtotal (95% CI)			**124**			**55**	**100.0%**	**-0.22 [-0.54 , 0.10]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.37 (P = 0.17)								
1.1.7 Cromolyn								
Vessal 2010	-7.78	2.54	20	-2.98	4.4	20	100.0%	-1.31 [-2.00 , -0.62]
Subtotal (95% CI)			**20**			**20**	**100.0%**	**-1.31 [-2.00 , -0.62]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.72 (P = 0.0002)								
1.1.8 Nicotinamide								
Omidian 2013	-1.2	1.65	25	-1.67	1.17	25	100.0%	0.32 [-0.23 , 0.88]
Subtotal (95% CI)			**25**			**25**	**100.0%**	**0.32 [-0.23 , 0.88]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.14 (P = 0.26)								
1.1.9 EPO								



Analysis 1.1. (Continued)

1.1.9 EPO								
De Marchi 1992	-16	27.7	10	-1.5	27.7	10	100.0%	-0.50 [-1.39 , 0.39]
Subtotal (95% CI)			**10**			**10**	**100.0%**	**-0.50 [-1.39 , 0.39]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.10 (P = 0.27)								
1.1.10 Cholestyramine								
Silverberg 1977	-0.48	0.415	5	-0.72	0.676	5	50.0%	0.39 [-0.87 , 1.65]
van Leusen 1978	-0.72	0.41	5	-0.48	0.68	5	50.0%	-0.39 [-1.64 , 0.87]
Subtotal (95% CI)			**10**			**10**	**100.0%**	**0.00 [-0.89 , 0.89]**
Heterogeneity: Tau² = 0.00; Chi² = 0.72, df = 1 (P = 0.39); I² = 0%								
Test for overall effect: Z = 0.00 (P = 1.00)								
1.1.11 Montelukast								
Nasrollahi 2007	-16.1	6.9201	7	-7.1	7.1363	7	16.3%	-1.20 [-2.37 , -0.03]
Mahmudpour 2017	-3.7	2.2	36	-0.53	2.17	37	83.7%	-1.44 [-1.95 , -0.92]
Subtotal (95% CI)			**43**			**44**	**100.0%**	**-1.40 [-1.87 , -0.92]**
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.72); I² = 0%								
Test for overall effect: Z = 5.78 (P < 0.00001)								
1.1.12 Sertraline								
Pakfetrat 2018	-5.5	3.11	25	-3.7	3.25	21	100.0%	-0.56 [-1.15 , 0.03]
Subtotal (95% CI)			**25**			**21**	**100.0%**	**-0.56 [-1.15 , 0.03]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.84 (P = 0.07)								
1.1.13 Lidocaine								
Tapia 1977	-0.8	0.63	10	-0.166	0.91	6	100.0%	-0.81 [-1.87 , 0.25]
Subtotal (95% CI)			**10**			**6**	**100.0%**	**-0.81 [-1.87 , 0.25]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.49 (P = 0.14)								
1.1.14 Gabapentin versus pregabalin								
Solak 2012	-4.41	2.43	20	-4.44	2.71	20	100.0%	0.01 [-0.61 , 0.63]
Subtotal (95% CI)			**20**			**20**	**100.0%**	**0.01 [-0.61 , 0.63]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.04 (P = 0.97)								
1.1.15 GABA analogues versus doxepin								
Foroutan 2017	-5.4	2.95	37	-2.9	2.91	35	100.0%	-0.84 [-1.33 , -0.36]
Subtotal (95% CI)			**37**			**35**	**100.0%**	**-0.84 [-1.33 , -0.36]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.42 (P = 0.0006)								
Test for subgroup differences: Chi² = 158.58, df = 14 (P < 0.00001), I² = 91.2%								

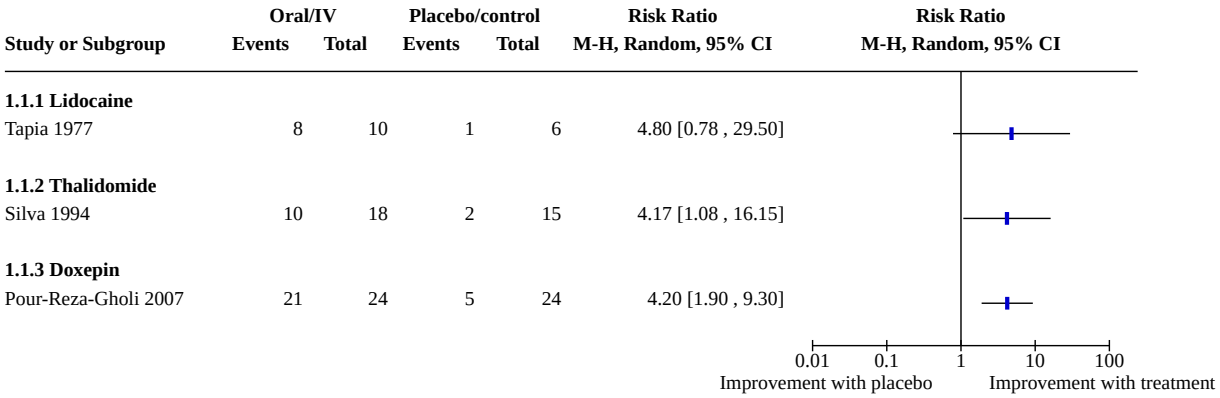


Footnotes

(1) Study 2 (cross-over RCT)

(2) Study 1 (parallel RCT)

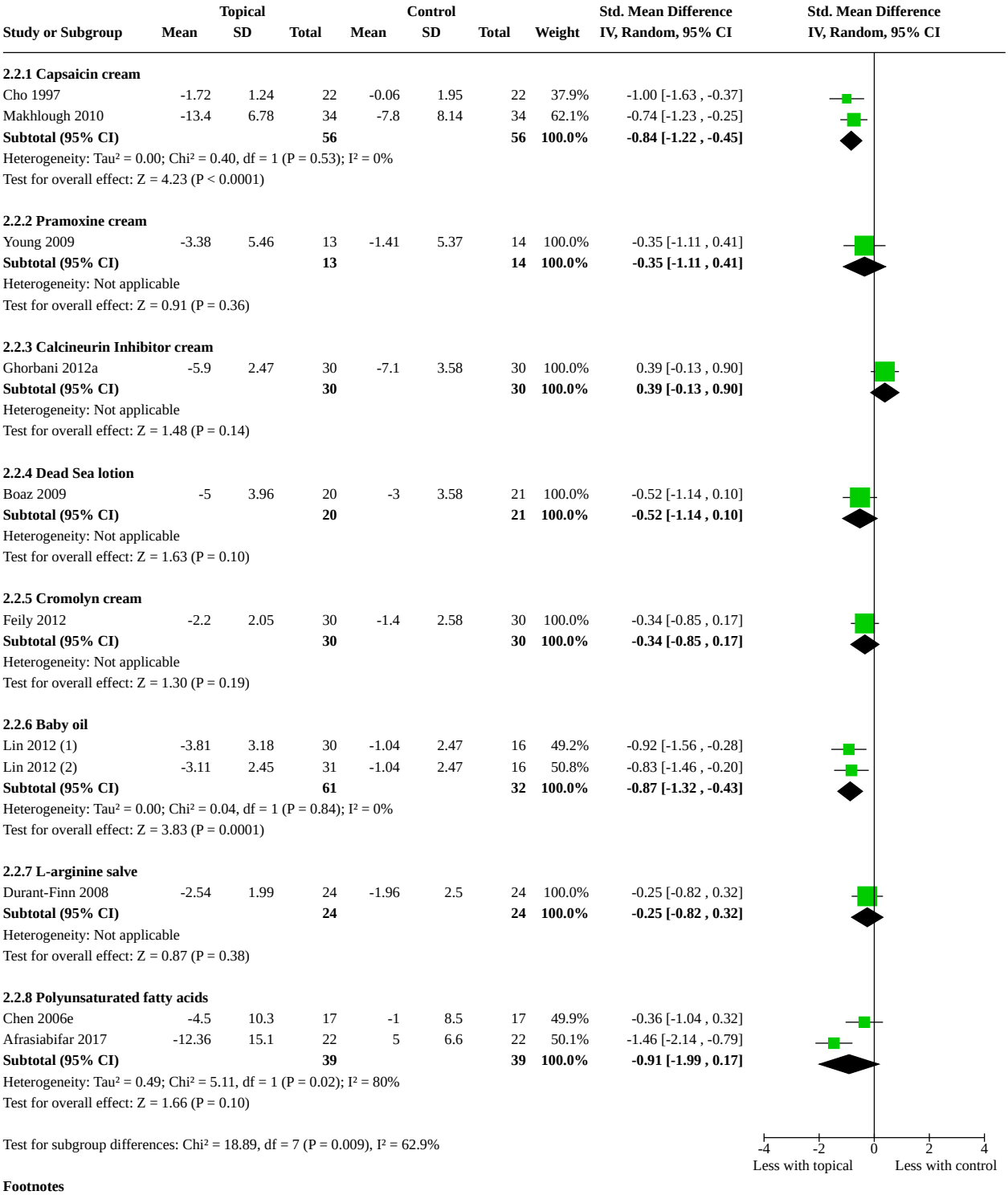
Analysis 1.2. Comparison 1: Pharmacological interventions (oral or IV), Outcome 2: Itch (dichotomous)



Comparison 2. Topical interventions

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Itch	10		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1.1 Capsaicin cream	2	112	Std. Mean Difference (IV, Random, 95% CI)	-0.84 [-1.22, -0.45]
2.1.2 Pramoxine cream	1	27	Std. Mean Difference (IV, Random, 95% CI)	-0.35 [-1.11, 0.41]
2.1.3 Calcineurin Inhibitor cream	1	60	Std. Mean Difference (IV, Random, 95% CI)	0.39 [-0.13, 0.90]
2.1.4 Dead Sea lotion	1	41	Std. Mean Difference (IV, Random, 95% CI)	-0.52 [-1.14, 0.10]
2.1.5 Cromolyn cream	1	60	Std. Mean Difference (IV, Random, 95% CI)	-0.34 [-0.85, 0.17]
2.1.6 Baby oil	1	93	Std. Mean Difference (IV, Random, 95% CI)	-0.87 [-1.32, -0.43]
2.1.7 L-arginine salve	1	48	Std. Mean Difference (IV, Random, 95% CI)	-0.25 [-0.82, 0.32]
2.1.8 Polyunsaturated fatty acids	2	78	Std. Mean Difference (IV, Random, 95% CI)	-0.91 [-1.99, 0.17]

Analysis 2.1. Comparison 2: Topical interventions, Outcome 1: Itch



Study or Subgroup	Topical Mean	Topical SD	Topical Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.2.1 Capsaicin cream								
Cho 1997	-1.72	1.24	22	-0.06	1.95	22	37.9%	-1.00 [-1.63 , -0.37]
Makhlough 2010	-13.4	6.78	34	-7.8	8.14	34	62.1%	-0.74 [-1.23 , -0.25]
Subtotal (95% CI)			**56**			**56**	**100.0%**	**-0.84 [-1.22 , -0.45]**
Heterogeneity: Tau² = 0.00; Chi² = 0.40, df = 1 (P = 0.53); I² = 0%								
Test for overall effect: Z = 4.23 (P < 0.0001)								
2.2.2 Pramoxine cream								
Young 2009	-3.38	5.46	13	-1.41	5.37	14	100.0%	-0.35 [-1.11 , 0.41]
Subtotal (95% CI)			**13**			**14**	**100.0%**	**-0.35 [-1.11 , 0.41]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.91 (P = 0.36)								
2.2.3 Calcineurin Inhibitor cream								
Ghorbani 2012a	-5.9	2.47	30	-7.1	3.58	30	100.0%	0.39 [-0.13 , 0.90]
Subtotal (95% CI)			**30**			**30**	**100.0%**	**0.39 [-0.13 , 0.90]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.48 (P = 0.14)								
2.2.4 Dead Sea lotion								
Boaz 2009	-5	3.96	20	-3	3.58	21	100.0%	-0.52 [-1.14 , 0.10]
Subtotal (95% CI)			**20**			**21**	**100.0%**	**-0.52 [-1.14 , 0.10]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.63 (P = 0.10)								
2.2.5 Cromolyn cream								
Feily 2012	-2.2	2.05	30	-1.4	2.58	30	100.0%	-0.34 [-0.85 , 0.17]
Subtotal (95% CI)			**30**			**30**	**100.0%**	**-0.34 [-0.85 , 0.17]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.30 (P = 0.19)								
2.2.6 Baby oil								
Lin 2012 (1)	-3.81	3.18	30	-1.04	2.47	16	49.2%	-0.92 [-1.56 , -0.28]
Lin 2012 (2)	-3.11	2.45	31	-1.04	2.47	16	50.8%	-0.83 [-1.46 , -0.20]
Subtotal (95% CI)			**61**			**32**	**100.0%**	**-0.87 [-1.32 , -0.43]**
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%								
Test for overall effect: Z = 3.83 (P = 0.0001)								
2.2.7 L-arginine salve								
Durant-Finn 2008	-2.54	1.99	24	-1.96	2.5	24	100.0%	-0.25 [-0.82 , 0.32]
Subtotal (95% CI)			**24**			**24**	**100.0%**	**-0.25 [-0.82 , 0.32]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.87 (P = 0.38)								
2.2.8 Polyunsaturated fatty acids								
Chen 2006e	-4.5	10.3	17	-1	8.5	17	49.9%	-0.36 [-1.04 , 0.32]
Afrasiabifar 2017	-12.36	15.1	22	5	6.6	22	50.1%	-1.46 [-2.14 , -0.79]
Subtotal (95% CI)			**39**			**39**	**100.0%**	**-0.91 [-1.99 , 0.17]**
Heterogeneity: Tau² = 0.49; Chi² = 5.11, df = 1 (P = 0.02); I² = 80%								
Test for overall effect: Z = 1.66 (P = 0.10)								
Test for subgroup differences: Chi² = 18.89, df = 7 (P = 0.009), I² = 62.9%								

Std. Mean Difference IV, Random, 95% CI

-4 -2 0 2 4

Less with topical Less with control

Footnotes

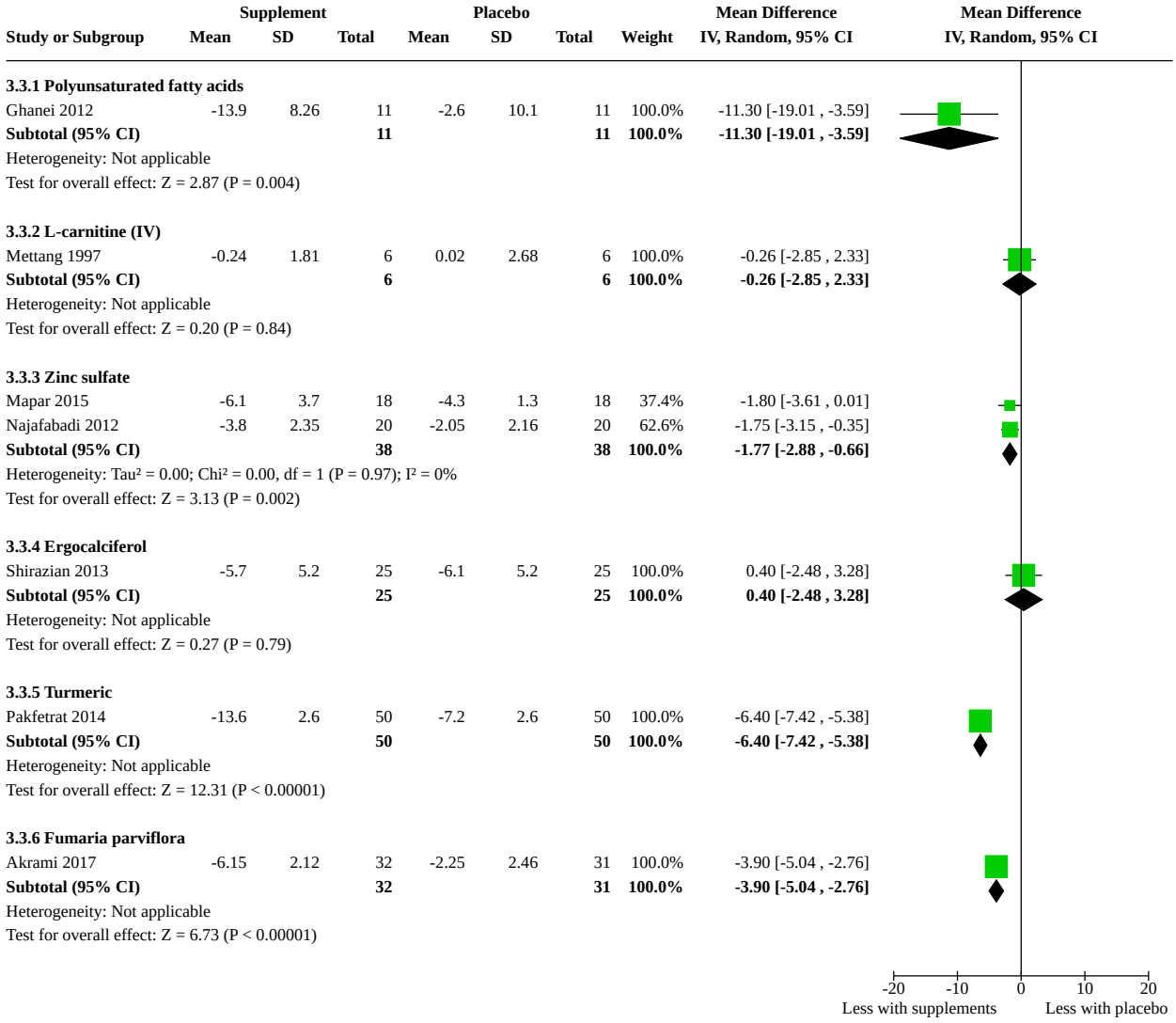
(1) Chilled

(2) Unchilled

Comparison 3. Oral or IV supplements

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Itch	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1.1 Polyunsaturated fatty acids	1	22	Mean Difference (IV, Random, 95% CI)	-11.30 [-19.01, -3.59]
3.1.2 L-carnitine (IV)	1	12	Mean Difference (IV, Random, 95% CI)	-0.26 [-2.85, 2.33]
3.1.3 Zinc sulfate	2	76	Mean Difference (IV, Random, 95% CI)	-1.77 [-2.88, -0.66]
3.1.4 Ergocalciferol	1	50	Mean Difference (IV, Random, 95% CI)	0.40 [-2.48, 3.28]
3.1.5 Turmeric	1	100	Mean Difference (IV, Random, 95% CI)	-6.40 [-7.42, -5.38]
3.1.6 Fumaria parviflora	1	63	Mean Difference (IV, Random, 95% CI)	-3.90 [-5.04, -2.76]

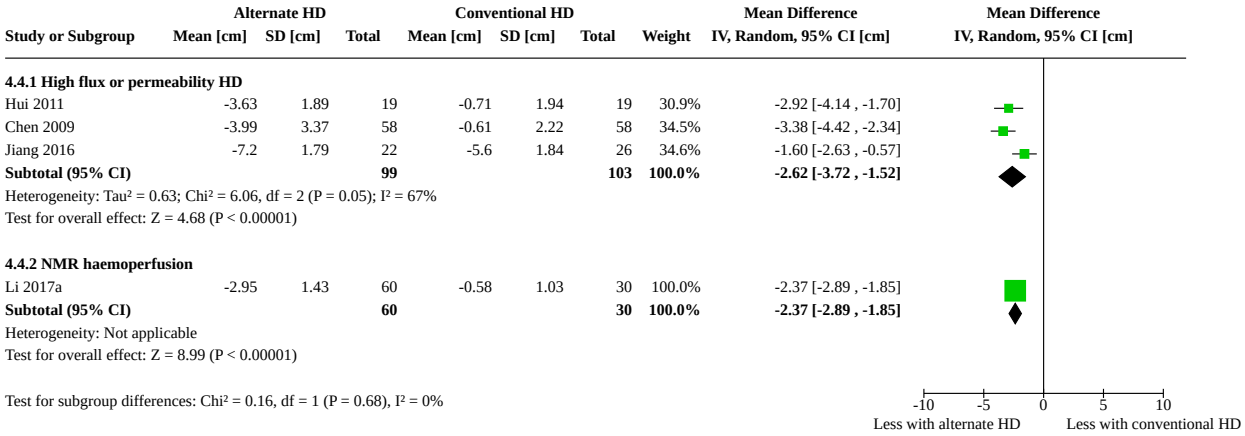
Analysis 3.1. Comparison 3: Oral or IV supplements, Outcome 1: Itch



Comparison 4. Haemodialysis modality

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Itch	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1.1 High flux or permeability HD	3	202	Mean Difference (IV, Random, 95% CI)	-2.62 [-3.72, -1.52]
4.1.2 NMR haemoperfusion	1	90	Mean Difference (IV, Random, 95% CI)	-2.37 [-2.89, -1.85]

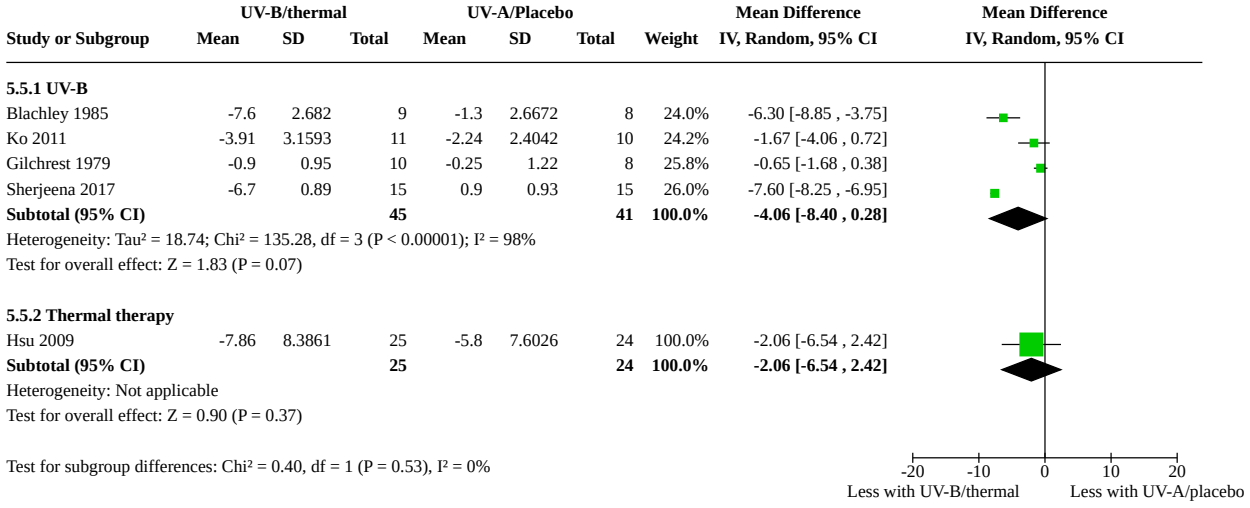
Analysis 4.1. Comparison 4: Haemodialysis modality, Outcome 1: Itch



Comparison 5. Other interventions

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Itch	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1.1 UV-B	4	86	Mean Difference (IV, Random, 95% CI)	-4.06 [-8.40, 0.28]
5.1.2 Thermal therapy	1	49	Mean Difference (IV, Random, 95% CI)	-2.06 [-6.54, 2.42]

Analysis 5.1. Comparison 5: Other interventions, Outcome 1: Itch



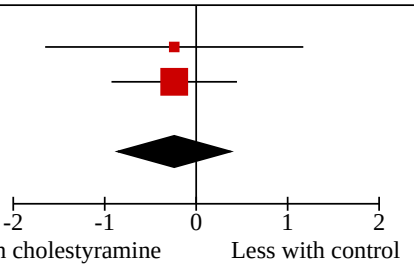
Comparison 6. Cross-over studies with paired data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Cholestyramine	2		Mean Difference (IV, Random, 95% CI)	-0.24 [-0.86, 0.38]

Analysis 6.1. Comparison 6: Cross-over studies with paired data, Outcome 1: Cholestyramine

Study or Subgroup	MD	SE	Weight	Mean Difference IV, Random, 95% CI
van Leusen 1978	-0.24	0.72	19.1%	-0.24 [-1.65 , 1.17]
Silverberg 1977	-0.24	0.35	80.9%	-0.24 [-0.93 , 0.45]
Total (95% CI)			**100.0%**	**-0.24 [-0.86 , 0.38]**

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.76 (P = 0.45)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Adverse events: pharmacological interventions

Intervention	Participants (studies)	Route/dose	Intervention adverse effects (dropouts/participants)*	Control adverse effects (dropouts/participants)*
GABA analogue (pregabalin or gabapentin) versus placebo	271 (6)	Pregabalin (a) Oral: 75 mg, twice/week Gabapentin (b) Oral: 400 mg, twice/week (c) Oral: 300 mg, 3 times/week (d) Oral: 300 mg/day (e) Oral: dose not reported	Gunal 2004 (c): somnolence, dizziness, fatigue Naghibi 2007 (e): somnolence Naini 2007 (b): somnolence, dizziness, nausea Nofal 2016 (d): somnolence (9/27), dizziness (5/27) Tol 2010 (c): not reported Yue 2015 (a): somnolence (3/67), loss of balance (2/67)	Gunal 2004: not reported Naghibi 2007: not reported Naini 2007: not reported Nofal 2016: not reported Tol 2010: not reported Yue 2015: not reported
Ondansetron versus placebo	161 (3)	(a) Oral: 8 mg, 3 times/day (b) Oral: 8 mg, once/day (c) Oral: 8 mg, twice/day	Ashmore 2000 (a): not reported Murphy 2003 (b): constipation (1/14), ischaemic stroke (1/18), line sepsis (1/17) Yue 2015 (c): nausea and vomiting (2/64)	Ashmore 2000: not reported Murphy 2003: not reported Yue 2015: none

Table 1. Adverse events: pharmacological interventions *(Continued)*

Kappa opioid agonists versus placebo	626 (4)	Nalfurafine (a) Oral: 2.5 µg once/day (b) Oral: 5 µg once/day (c) IV: 5 µg, 3 times/week (d) IV: 2.5, 5 µg with dialysis CR845 (e) IV: 0.5 to 1.5 µg/kg with dialysis	Kumagai 2010 (a, b) 2.5 µg (oral): somnolence (4.5%); insomnia (7.1%), diarrhoea (4.5%), nasopharyngitis (8.0%) 5 µg (oral): constipation (7.9%), somnolence (3.5%), insomnia (14.9%), nasopharyngitis (12.3%) Spencer 2015 (e): not reported Spencer 2017 (e) (0.5 to 1.5 µg/kg): somnolence (9/129), dizziness (12/129), headache (5/129), diarrhoea (16/129), nausea (11/129) Bhaduri 2006 (d): not reported Wikstrom 2005 (c): headache (3/26), nausea (3/26), vomiting (2/26), insomnia (2/26), vertigo (2/26)	Kumagai 2010: nasopharyngitis (17.1%), headache (3.6%), vomiting (3.6%) Spencer 2015: not reported Spencer 2017: somnolence (1/45), dizziness (2/45), headache (1/45), diarrhoea (0/45) Wikstrom 2005: 13/25 (type not reported)
Mu opioid antagonists versus placebo	31 (2)	Oral: 50 mg once/day	Pauli-Magnus 2000: loss of appetite and nausea (9) Peer 1996: heartburn (2), abdominal discomfort (3)	Pauli-Magnus 2000: nausea (1) Peer 1996: not reported
Nalbuphine versus placebo	373 (1)	Oral: 60 or 120 mg, twice/day	TREVITR02 2017 60 mg: serious adverse events (12.7%), adverse events leading to discontinuation (33/128) 120 mg: serious adverse events (6.7%), adverse events leading to discontinuation (27/120)	TREVITR02 2017: serious adverse events (15.4%), adverse events leading to discontinuation (7/123)
EPO versus placebo	39 (2)	(a) IV: 36 U/kg/dialysis (b) SC: 2000 IU twice/day	De Marchi 1992 (a): not reported Sja'bani 1997 (b): not reported	De Marchi 1992: not reported Sja'bani 1997: not reported
Nicotinamide versus placebo	50 (1)	Oral: 500 mg twice/day	Omidian 2013: not reported	Omidian 2013: not reported
Lidocaine versus placebo	20 (1)	IV: 200 mg	Tapia 1977: not reported	Tapia 1977: not reported
Cholestyramine	20 (2)	Oral: 5 mg, twice/day	Silverberg 1977: constipation (1/5), nausea (1/5) van Leusen 1978: not reported	Silverberg 1977: not reported van Leusen 1978: not reported
Montelukast versus placebo	89 (2)	Oral: 10 mg/day	Mahmudpour 2017: not reported Nasrollahi 2007: myelodysplastic syndrome (1/8)	Mahmudpour 2017: Not reported

Table 1. Adverse events: pharmacological interventions *(Continued)*

				Nasrollahi 2007: myocardial infarction (1/8)
Sertraline versus placebo	50 (1)	Oral: 50 mg twice/day	Pakfetrat 2018: not reported	Pakfetrat 2018: not reported
Sodium thiosulfate versus placebo	45 (1)	IV: 12.5 mg/dialysis session	Mohamed 2012: not reported	Mohamed 2012: not reported
Doxepin versus placebo	24 (1)	Oral: 10 mg, twice/day	Pour-Reza-Gholi 2007: drowsiness (12/24)	Pour-Reza-Gholi 2007: not reported
Thalidomide versus placebo	29 (1)	Oral: 100 mg/day	Silva 1994: not reported	Silva 1994: not reported
Cimetidine versus placebo	13 (1)	Oral: 600 mg/day	Aubia 1980: not reported	Aubia 1980: not reported
Cromolyn versus placebo	62 (1)	Oral: 135 mg, 3 times/day	Vessal 2010: flatulence (1/32)	Vessal 2010: nausea (5/30), diarrhoea (4/30)
Gabapentin versus pregabalin	50 (1)	Oral gabapentin (300 mg, once/day) versus oral pregabalin (75 mg, once/day)	Solak 2012 Gabapentin: not reported Pregabalin: not reported	--
GADA versus ondansetron	131 (1)	Oral pregabalin (75 mg twice/week) versus oral ondansetron (8 mg/day)	Yue 2015 Pregabalin: somnolence (3/67), loss of balance (2/67) Ondansetron: not reported	--
GABA analogue versus doxepin	90 (1)	Oral pregabalin (50 mg every other night) versus oral doxepin (10 mg/night)	Foroutan 2017 Pregabalin: intolerable adverse events (3/46), somnolence (6/37), oedema (3/37), drowsiness (3/27), imbalance (1/37), numbness (1/37) Doxepin: intolerable adverse events (1/44), nervousness (1/35)	--
GABA analogue versus antihistamine	212 (4)	(a) Oral gabapentin (100 mg/day) versus oral ketotifen (1 mg, twice/day) (b) Oral gabapentin (300 mg, 3 times/week) versus oral dexchlorpheniramine (6 mg, 3 times/week) (c) Oral gabapentin (300 mg/day) versus oral loratadine (10 mg/day)	Amirkhanlou 2016 (a) Gabapentin: drowsiness (4/26), dizziness (1/26) Ketotifen: drowsiness (4/26), dizziness (1/26) Gobo-Oliveira 2018 (b) Gabapentin: total (11/30), drowsiness (17%) Dexchlorpheniramine: total (8/30), drowsiness (1/30)	--

Table 1. Adverse events: pharmacological interventions *(Continued)*

		(d) Oral gabapentin (100 to 200 mg/day) versus oral hydroxyzine (10 mg/day) (e) Oral gabapentin (100 mg/day) versus oral hydroxyzine (10 mg/day)	Marin 2013 (c) Gabapentin: somnolence (8/30) Loratadine: none reported Noshad 2011 (d) Gabapentin: complications (7/20) Hydroxyzine: complications (10/20) Suwanpidokkul 2007 (e) Gabapentin: (9/18) Loratadine: (4/16)	
Mu opioid antagonists versus antihistamine	52 (1)	Oral naltrexone (50 mg/day) versus oral loratadine (10 mg/day)	Legroux-Crespel 2004 Naltrexone (26): vomiting (2), nausea (9), anorexia (1), abdominal distention (1), malaise (1), cramps (2), sleep disturbances (5), vertigo (5), headache (2), somnolence (1), paraesthesia (1), withdrawn (10) Loratadine (26): vomiting (2), malaise (1), withdrawn from study (2)	--
Ondansetron versus antihistamine	20 (1)	(a) Ondansetron tablet (8 mg/day) versus cyproheptadine syrup (8 mg/day) (b) "3 doses ondansetron 8mg" versus "diphenhydramine 25mg" (c) Oral ondansetron (8 mg, 3 times/day) versus oral loratadine (10 mg twice/day)	Ozaykan 2001 (a): not reported Subach 2001 (b): not reported Mirnezami 2013 (c): not reported	--

*when reported
GABA - gamma-aminobutyric acid

Table 2. Adverse events: topical interventions

Intervention	Participants (studies)	Route/dose	Intervention adverse effects (dropouts/participants)*	Control adverse effects (dropouts/participants)*
Cromolyn cream versus placebo	60 (1)	4% cream	Feily 2012: burning sensation (6/30)	Feily 2012: none
Capsaicin cream versus placebo	91 (4)	(a) 0.025%, 4 times/day (b) 0.03%, 4 times/day	Breneman 1992 (a): burning and stinging sensation (5), decrease in xerosis (3), dryness (2)	Breneman 1992: not reported

Table 2. Adverse events: topical interventions *(Continued)*

			Cho 1997 (a): not reported Makhlough 2010 (b): skin burning Tarng 1996 (a): local burning and/or stinging sensations	Cho 1997: not reported Makhlough 2010: none Tarng 1996: local burning and/or stinging sensations
Pramoxine lotion versus placebo	28 (1)	1.0% twice/day	Young 2009: none	Young 2009: none
Baby oil versus placebo	92 (1)	Chilled and unchilled 15 min application at least once/day	Lin 2012: not reported	Lin 2012: not reported
Dead Sea lotion versus placebo	50 (1)	Entire body, twice/day	Boaz 2009: total adverse events (2/25)	Boaz 2009: total adverse events (3/25)
Sericin cream versus placebo	50 (1)	1 g, twice/day	Aramwit 2012a: not reported	Aramwit 2012a: not reported
L-arginine salve versus placebo	24 (1)	25 µg/2.5 cm^2 twice/day	Durant-Finn 2008: not reported	Durant-Finn 2008: not reported
Calcineurin inhibitors versus placebo	80 (2)	TAC: 0.1% twice/day Pimecrolimus: 1.0% twice/day	Duque 2005: warmth sensation (6/12) Ghorbani 2012a: burning sensation which disappeared by the end of 8 weeks	Duque 2005: warmth sensation (3/8) Ghorbani 2012a: none
Sweet almond oil versus no intervention	44 (1)	100 mg/day	Afrasiabifar 2017: not reported	Afrasiabifar 2017: not reported
Gamma-linoleic acid versus placebo	17 (1)	2.2%, 30 mL/day	Chen 2006e: allergic reaction (1/8)	Chen 2006e: none
Calcineurin inhibitors versus cromolyn	60 (1)	Pimecrolimus: 2% twice/day Cromolyn: 4%, twice/day	Ghorbani Birgani 2011: unknown	Ghorbani Birgani 2011: unknown
Avena sativa versus diluted vinegar versus hydroxyzine	23 (1)	Avena sativa: variable dose, twice/day Dilute vinegar: 30 mL twice/day Oral hydroxyzine: 10 mg/day	Nakhaee 2015: not reported	--
Sarna versus eurax	30 (1)	Sarna: 0.5% each of camphor, menthol, and phenol "as required" for 7 days Eurax: 10% crotamiton "as required" for 7 days	Tan 1990 Sarna: none Eurax: rash (1)	--

*when reported

Table 3. Adverse events: oral and IV supplements

Intervention	Participants (studies)	Dose/route	Intervention adverse effects (dropouts/participants)*	Placebo adverse effects (dropouts/participants)*
Polyunsaturated fatty acids versus placebo	89 (4)	Fish oil (a) Oral: 6 g/day (b) Oral: 3 g/day Omega-3 fatty acids (c) Oral: 3 g/day	Begum 2004 (a): not reported Ghanei 2012 (c): not reported Mojgan 2017 (b): not reported Peck 1996 (a): not reported	Begum 2004: not reported Ghanei 2012: not reported Mojgan 2017: not reported Peck 1996: not reported
L-carnitine versus placebo	17 (1)	IV: 10 mg/kg, once/day	Mettang 1997: not reported	Mettang 1997: not reported
Zinc sulfate versus placebo	80 (2)	(a) Oral: 220 mg/day (b) Oral: 200 mg twice/day	Mapar 2015 (a): none Najafabadi 2012 (b): none "attributable to zinc sulfate"	Mapar 2015: vomiting (1/20) Najafabadi 2012: not reported
Ergocalciferol versus placebo	50 (1)	Oral: 50,000 IU/week	Shirazian 2013: none	Shirazian 2013: not reported
Turmeric (curcumin) versus placebo	100 (1)	Oral: 500 mg (22.1 mg), 3 times/day	Pakfetrat 2014: none	Pakfetrat 2014: not reported
Fumaria parviflora versus placebo	79 (1)	Oral: 1000 mg, 3 times/day	Akrami 2017: Gastric pain (4/39), rash (1/39)	Akrami 2017: abdominal pain (1/40), constipation (1/40)
Senna versus placebo	60 (1)	Oral: dose and frequency not reported	Fallahzadeh 2015: not reported	Fallahzadeh 2015: not reported
Evening primrose oil	16 (1)	Oral: 2 capsules/day (containing 360 mg of linoleic acid, 50 mg oleic acid and 45 mg of gamma-linoleic acid)	Yoshimoto-Furuie 1999: none	Yoshimoto-Furuie 1999: none
Activated charcoal versus placebo	20 (1)	Oral: 6 g/day	Pederson 1980: not reported	Pederson 1980: not reported
Charcoal versus aluminium hydroxide	30 (1)	Charcoal: 6 g, 3 times/day Aluminium hydroxide: 30 mL, 3 times/day	Shariati 2010: not reported	--

*when reported

Table 4. Adverse events: dialysis modality

Intervention	Participants (studies)	Dose/route	Intervention adverse effects (dropouts/participants)*	Control adverse effects (dropouts/participants)*
High flux/ high permeability/high flow HD	252 (4)	(a) High-flow HD (b) High-permeability HD (c) High-flux HD	Aliasgharpour 2018 (a): not reported Chen 2009 (b): not reported Hui 2011 (c): not reported Jiang 2016 (c): not reported	Aliasgharpour 2018: not reported Chen 2009: not reported Hui 2011: not reported Jiang 2016: not reported
HD with haemoperfusion	90 (1)	Haemoperfusion HA130-RHA HA330-RHA	Li 2017a: not reported	Li 2017a: not reported
Haemoperfusion plus HD versus haemoperfusion plus HDF	40 (1)	Haemoperfusion plus HD Haemoperfusion plus HDF	Zhang 2016a Haemoperfusion plus HD: not reported Haemoperfusion plus HDF: not reported	--
Magnesium-free HD versus standard HD	17 (1)	Standard HD: 0.85 mmol/L magnesium solution for 2 weeks	Carmichael 1988: not reported	Carmichael 1988: not reported
Calcium dialysate HD	4 (1)	Calcium concentration 1.0 mmol/L 1.25 mmol/L 1.75 mmol/L	Kyriazis 2000: not reported	Kyriazis 2000: not reported
Cool versus normal dialysate	60 (1)	Cool dialysate: 35.5ºC, 3 times/week Normal dialysate: 37ºC, 3 time/week	Rad 2017: not reported	Rad 2017: not reported

*when reported

Table 5. Adverse events: other interventions

Intervention	Participants (studies)	Dose/route	Intervention adverse effects (dropouts/participants)*	Control adverse effects (dropouts/participants)*
UV-B exposure	75 (4)	(a) 0.19 nJ/cm^2/sec, 3 times/week	Blachley 1985 (a): not reported	Blachley 1985: not reported

Table 5. Adverse events: other interventions *(Continued)*

		(b) Minimal erythema dose, twice/week (c) 4.4 watts/m^2, twice/week (d) 200 mJ/cm^2, 3 times/week	Chan 1995 (b): not reported Gilchrest 1977 (c): sunburn (3/10), tanning (5/10) Gilchrest 1979 (c): mild sunburn and tanning Ko 2011 (d): erythema (2/11)	Chan 1995: not reported Gilchrest 1977: not reported Gilchrest 1979: not reported Ko 2011: not reported
UV-A exposure	11 (1)	UV-A (exposure): 40 min exposure (10, 180 cm 85W UV-A lamps) 3 times/week	Taylor 1983: not reported	Taylor 1983: not reported
Thermal therapy	41 (1)	40ºC thermal therapy, twice/week	Hsu 2009: not reported	Hsu 2009: not reported
UV-B exposure versus cetirizine	30 (1)	UV-B Whole body: 200 to 1038 mJ/cm^2 every 3rd day for 15 sessions Cetirizine Oral: 10 mg/day for the same duration	Sherjeena 2017: not reported	--

*when reported

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. pruritus:ti,ab,kw 2. pruritis:ti,ab,kw 3. pruritic:ti,ab 4. itch*:ti,ab,kw 5. #1 or #2 or #3 or #4 6. "renal replacement therapy":ti,ab,kw 7. dialysis:ti,ab,kw 8. he*modialysis:ti,ab,kw 9. he*mofiltration:ti,ab,kw 10.he*modiafiltration:ti,ab,kw 11.(PD or CAPD or CCPD or APD):ti,ab 12.(kidney next disease*):ti,ab,kw 13.(kidney next failure):ti,ab,kw 14.(renal next insufficiency):ti,ab,kw 15.ur*emi*:ti,ab,kw 16.(CKD or CKF or CRD or CRF or ESRD or ESRF or ESKD or ESKF):ti,ab 17.(renal next disease):ti,ab,kw

(Continued)

	18.(renal next failure):ti,ab,kw 19.#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 20.#5 and #19
MEDLINE	1. Pruritus/ 2. pruritus.tw. 3. pruritis.tw. 4. pruritic.tw. 5. itch$.tw. 6. or/1-5 7. Renal Insufficiency/ 8. exp Renal Insufficiency, Chronic/ 9. Kidney Diseases/ 10.exp Renal Dialysis/ 11.Uremia/ 12.(kidney disease or kidney failure or renal disease or renal failure).tw. 13.(CKD or CKF or CRD or CRF or ESRD or ESRF or ESKD or ESKF).tw. 14.dialysis.tw. 15.(hemodialysis or haemodialysis).tw. 16.(hemofiltration or haemofiltration).tw. 17.(hemodialfiltration or haemodiafiltration).tw. 18.(CAPD or CCPD or APD).tw. 19.ur?emi$.tw. 20.or/7-18 21.and/6,20
EMBASE	1. Pruritus/ 2. pruritus.tw. 3. pruritis.tw. 4. pruritic.tw. 5. itch$.tw. 6. or/1-5 7. exp Renal Replacement Therapy/ 8. mild renal impairment/ 9. stage 1 kidney disease/ 10.moderate renal impairment/ 11.severe renal impairment/ 12.end stage renal disease/ 13.renal replacement therapy-dependent renal disease/ 14.(hemodialysis or haemodialysis).tw. 15.(hemofiltration or haemofiltration).tw. 16.(hemodiafiltration or haemodiafiltration).tw. 17.dialysis.tw. 18.(CAPD or CCPD or APD).tw. 19.Kidney Disease/ 20.Chronic Kidney Disease/ 21.Kidney Failure/ 22.Chronic Kidney Failure/ 23.Uremia/ 24.(kidney disease or kidney failure or renal disease or renal failure).tw. 25.(CKD or CKF or CRD or CRF or ESRD or ESRF or ESKD or ESKF).tw. 26.ur?emi$.tw.

(Continued)

	27.or/7-26 28.and/6,27

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Incomplete outcome data	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with ob-

(Continued)

Attrition bias due to amount, nature or handling of incomplete outcome data.	served event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

HISTORY

Protocol first published: Issue 11, 2014
Review first published: Issue 12, 2020

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: DH, SJ
2. Study selection: DH, SJ
3. Extract data from studies: DH
4. Enter data into RevMan: DH
5. Carry out the analysis: DH, AW
6. Interpret the analysis: DH
7. Draft the final review: DH, AW
8. Disagreement resolution: AW
9. Update the review: DH

DECLARATIONS OF INTEREST

- Daniel Hercz: none known
- Simon H Jiang: none known
- Angela C Webster: none known

INDEX TERMS

Medical Subject Headings (MeSH)

Analgesics [*therapeutic use]; Antipruritics [*therapeutic use]; Pruritus [*drug therapy] [etiology]; Randomized Controlled Trials as Topic; Renal Dialysis [methods]; Renal Insufficiency, Chronic [*complications] [therapy]

MeSH check words

Humans